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INNERVATION OF THE THYROID GLAND

I. THE PRESENCE OF GANGLIA IN THE THYROID OF THE DOG *

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NEW YORK

In spite of the voluminous literature that has accumulated during the last thirty years on the subject of the structure, physiology and pathology of the thyroid, the knowledge concerning the innervation of this endocrine gland is meager. Credit is due to physiologists for their efforts to ascertain the extent of the influence of the nervous system on the activities of the gland, but, unfortunately, the conclusions drawn from their experiments are for the most part contradictory or open to serious criticism. On the other hand, the anatomic evidence is very unsatisfactory. Histologic studies undertaken by several investigators have been based, without exception, on glands with an intact nerve supply. The valuable analytic methods that have thrown so much light on the structure of the nervous system, and more especially on the connections of its neurons, have never been applied to the thyroid. In the absence of experimental evidence, too much emphasis has been placed on the problem of the mode of termination of the fibers within the gland, and little or no attention has been paid to the origin of the fibers.

For the last three years I have sought to gain a more intimate knowledge of the origin and distribution of the nerves of the thyroid in a few of the laboratory animals. But, instead of limiting the study to preparations of adult thyroids, I have examined the glands of fetuses, new-born and young animals. As a necessary complement, I have also undertaken experiments on secondary degeneration of the nerves. The results of this work will be reported in several papers. The present article deals with the structure of ganglia found in the thyroid of the dog.

The presence of ganglion cells in the mammalian thyroid, reported by Peremeschko,[1] and Poincaré,[2] in preparations of teased glands, and later by Crisafulli [3] and Sacerdotti [4] in sections impregnated with the

* Submitted for publication, Jan. 19, 1931.

* From the Department of Anatomy, Cornell University Medical College, aided by the Johnston Livingston Fund for Experimental Biochemistry.

1. Peremeschko: Ztschr. f. wissensch. Zool. **17**:279, 1867.

2. Poincaré, M.: J. d'anat. et physiol. **11**:477, 1875.

3. Crisafulli, E.: Boll. mens. dell' Accad. Gioenia di sc. naz., Catania, 1892, vol. 25.

4. Sacerdotti, C.: Internat. Monatschr. f. Anat. u. Physiol. **11**:326, 1894.

silver chromate method of Golgi, has been denied by all subsequent investigators (Anderson,[5] Berkeley,[6] Briau,[7] Trautmann,[8] Zeiss,[9] Rhinehart[10]). Structures resembling ganglion cells in Golgi slides have been variously regarded as precipitates or as impregnated lemmoblasts and connective tissue elements. In a recent paper, Popow[11] stated his views on the subject in unequivocal terms. According to this author, the reputed neurons are "Artefakte in der Form derselben dreieckigen varikösen Verdickungen deren Beispiel speziell die Abb. 6 bietet" (artefacts in the shape of the same triangular varicose thickenings, an example of which is shown in fig. 6). And he added: "es ist möglich dass solche Bildungen den alten Autoren anlass zu falschen Schlüssen geben konnten" (it is possible that such formations were the cause of the incorrect conclusions made by older authors).

In a previous contribution,[12] I have reported the presence of ganglion cells and their association with nerve fibers in the thyroids of adult dogs. The glands were impregnated by the method of Golgi, but since this procedure is not well adapted to the study of the finer structural details of the nerve cells I decided to use the reduced silver nitrate method of Cajal. Furthermore, in order to overcome difficulties of technic and to obtain serial sections of whole lobes, the method was applied to the thyroids of puppies from birth to the age of 6 or 7 months. With this technic it has been possible to demonstrate the existence of nerve cells and their association into ganglia, as shown by the descriptions and figures in the following pages.

The glands were fixed in several mixtures (alcohol-ammonia alcohol-chloral hydrate, alcohol-chloral hydrate-nitric acid), impregnated with silver nitrate (from four to six days, at 38 C.), embedded in paraffin and cut into serial sections. Toning with gold chloride was found useful in many cases, especially since the follicular cells are intensely argyrophilic. By the use of the gold chloride, too dark backgrounds were avoided.

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5. Anderson, O. A.: Arch. f. Anat., 1894, p. 177.

6. Berkeley, H. J.: Johns Hopkins Hosp. Rep. **4**:281, 1894.

7. Briau, E.: Thèse de Lyon, Paris; cited in Centralbl. f. chir. **25**:274, 1898.

8. Trautmann, T. M.: Inaug. Dis., Halle-Wittenberg. Gruben, A. Koenig, 1895; quoted by Popow, N. A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **115**:131, 1928.

9. Zeiss, O.: Inaug. Dis., Strassburg, 1877; quoted by Anderson (footnote 5).

10. Rhinehart, D. A.: Am. J. Anat. **13**:91, 1912.

11. Popow, N. A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **110**:383, 1927; **115**:131, 1928.

12. Nonidez, J. F.: The Vegetative Nervous System, New York, Association for Research in Nervous and Mental Diseases, 1930, p. 366.

The photomicrographs included in some of the figures are intended to show the position of the ganglia in the parenchyma, and their general structure. Their finer structural details are shown in the drawings, in which several planes have been represented. All the drawings were made under an oil immersion lens (Zeiss apochromatic 2 mm.).

DISTRIBUTION OF THE GANGLIA

The position of the ganglia within the gland and their size are subject to individual variations. In addition to the ganglia, there are scattered neurons. The latter usually appear embedded in the parenchyma (interstitial neurons) or are applied against the walls of the arteries (periarterial neurons).

In general, it can be said that in the dog the ganglia appear as swellings along the path of the main branches of the nerves. Groups of ganglion cells independent from the nerve trunks are found only in exceptional cases (fig. 6). The numbers of these swellings vary in different lobes. The highest number observed was seven. On the other hand, there are cases in which there is a single, large ganglion placed toward the center of the lobe (fig. 3). In one puppy, a large ganglion was found half embedded in the glandular parenchyma at the entrance of one of the main branches of a nerve of the thyroid.

The larger ganglia contain from ten to eighteen neurons of variable size. A few may be quite large, but medium-sized neurons seem to predominate. In new-born and very young puppies there are small, round cells which lack well developed dendrites and have a faintly staining neurofibrillar network. They are, in all probability, neuroblasts that have not completed their evolution.

Figure 1 represents one of the large ganglia of the thyroid of a new-born puppy. In this case the ganglion is located at the bifurcation of one of the main branches of a nerve (*n*) and is included in two sections. As will be noticed, the dendrites of the cells are directed toward the center of the ganglion. A thick preganglionic fiber (*p*) ending as a pericellular basket on a deeply stained, binucleate cell is clearly seen in the photomicrograph. The drawing shows that this fiber is accompanied by a thinner fiber apparently ending on the same cell.

Figure 2 shows a ganglion in transverse section. The center of the ganglion is occupied by nerve fibers, most of which appear in cross-section, and a delicate plexus of fibrils (collaterals and terminals of the fibers). The neurons are of diverse size, the larger elements somewhat resembling the monopolar cells of the cerebrospinal ganglia.

Figure 3 represents a large ganglion from the thyroid of a 6 months old puppy. The plexus of fibrils is more elaborate than in the ganglia

of the younger animals. The perineuronal spaces under the capsules surrounding the neurons are also more manifest.

While grouping of the neurons into definite ganglia seems to represent the usual condition, there are instances in which the neurons are irregularly scattered along the nerves. This arrangement may even occur in lobes possessing larger ganglionic swellings. An intermediate condition is seen in the small ganglia, in which only three or four neurons occur loosely grouped in the nerve bundle (fig. 4 and 5).

Groups of neuroblasts showing more or less developed neurofibrils may be already present in the lobes of the thyroid of fetuses measuring from 6 to 7 cm. The nerve fibers present in the fetal glands have not finished their growth, and often end in "growth clubs" (Cajal's mazas de crecimiento). As will be shown in another paper, the nerve fibers of the thyroid end on the walls of the arteries and arterioles. The growth of the fibers in fetal thyroids seems to keep pace with the development of the arterial branches, which at this stage are few in number.

STRUCTURE OF THE GANGLIA

The larger ganglia are surrounded by sheaths of connective tissue continuous with the perineurium. Each ganglion cell is enclosed within a capsule of connective tissue. Instances of two neurons occupying a single capsule were occasionally found. Intracapsular cells resembling amphicytes or satellite cells were noticed in several cases.

The neurons within the ganglia are of the long dendritic type and may appear somewhat elongated. In fairly round neurons the cell bodies measure from 16 to 25 microns. There are, however, larger cells, too irregularly shaped to be measured. In older puppies, the size of the cells correspondingly increases. Some of them are so large that it is surprising that they have never been detected in sections stained by routine methods. In medium-sized neurons, the nuclei are relatively large as compared with the volume of the cell body, and are usually oval. They measure from 10 to 13.5 microns in new-born or very young puppies. The smaller neurons have correspondingly smaller nuclei (from 6 to 7.5 microns), but the volume of the latter usually exceeds the volume of the nuclei of the follicular cells (from 5.5 to 6 microns or more in some cells). A nucleolus may be present in the larger nuclei.

The dendrites of the larger neurons nearly always arise from a restricted area of the cell body. In many cases there is a main dendritic prolongation that branches toward the center of the ganglion, and when the secondary branches are not contained in the section the neurons somewhat resemble the monopolar neurons of the cerebrospinal ganglia (fig. 2). Furthermore, when the main dendritic stem of the monopolar

cells is not included in the section, the cell bodies appear round or oval, as seen in one of the cells in figure 3. The monopolar aspect of the neurons seems to be largely influenced by their position in the periphery of the ganglia. In the larger ganglia, many cells are multipolar but have few dendrites.

The dendrites are for the most part sparsely branched, but there are instances of rather elaborate arborizations arising at variable

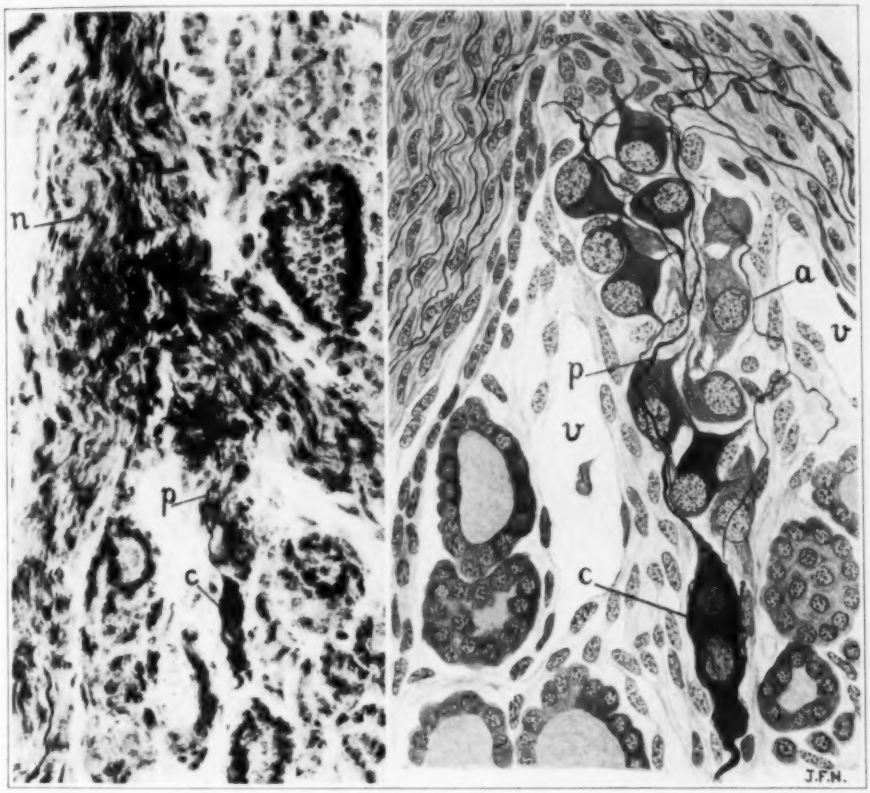

Fig. 1.—Photomicrograph and drawing of a ganglion of the thyroid of a newborn puppy: *a*, thin prolongation, probably the axon of neuron *c*; *n*, large branch of a nerve of the thyroid; *p*, preganglionic fiber ending as a pericellular basket around cell *c*; *v*, lymphatic vessels. Alcohol-ammonia fixation.

distances from the cell body (fig. 5,*c*). The arborizations end freely in the substance of the ganglion or are wrapped around the cell bodies of other neurons under the form of pericellular baskets or "nests" (fig. 7, *A*). Dendrites with flattened or lamellar aspect are not uncommon, and in some cases they possess club-shaped dilatations of considerable size. In other neurons the smaller branches, or twigs, end in

minute knobs, or in larger reticulated bulbs. The mode of termination of the dendritic arborizations in new-born or very young puppies is, in most cases, difficult to study since the neurofibrils are faintly stained. In older puppies, the final ramifications are more easily traced. As most of the dendrites are quite long, they may extend for some distance into the nerves, but they do not leave the ganglion to penetrate among the follicles.

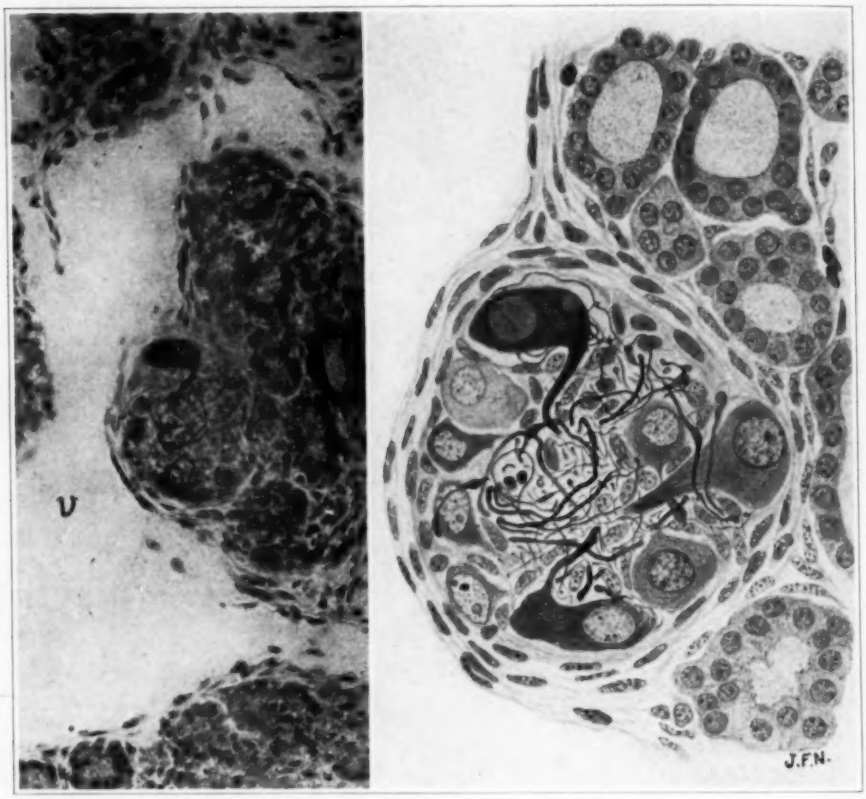

Fig. 2.—Photomicrograph and drawing of a ganglion seen in transverse section of a 2 days old puppy: *v*, section of a lymph vessel. Alcohol-chloral hydrate fixation.

In very young puppies, the neurofibrils of most neurons of the thyroid appear faintly impregnated. There are, however, exceptions to this rule, as may be seen in figures 2, 5, 6 and 7 *A*. This is especially true in those cases in which the pericellular baskets of axonic origin are impregnated (figs. 1 and 2). Under such conditions, the finer branches of the baskets cannot be easily distinguished from the coarse neurofibrils in the peripheral layer of cytoplasm of the neurons (super-

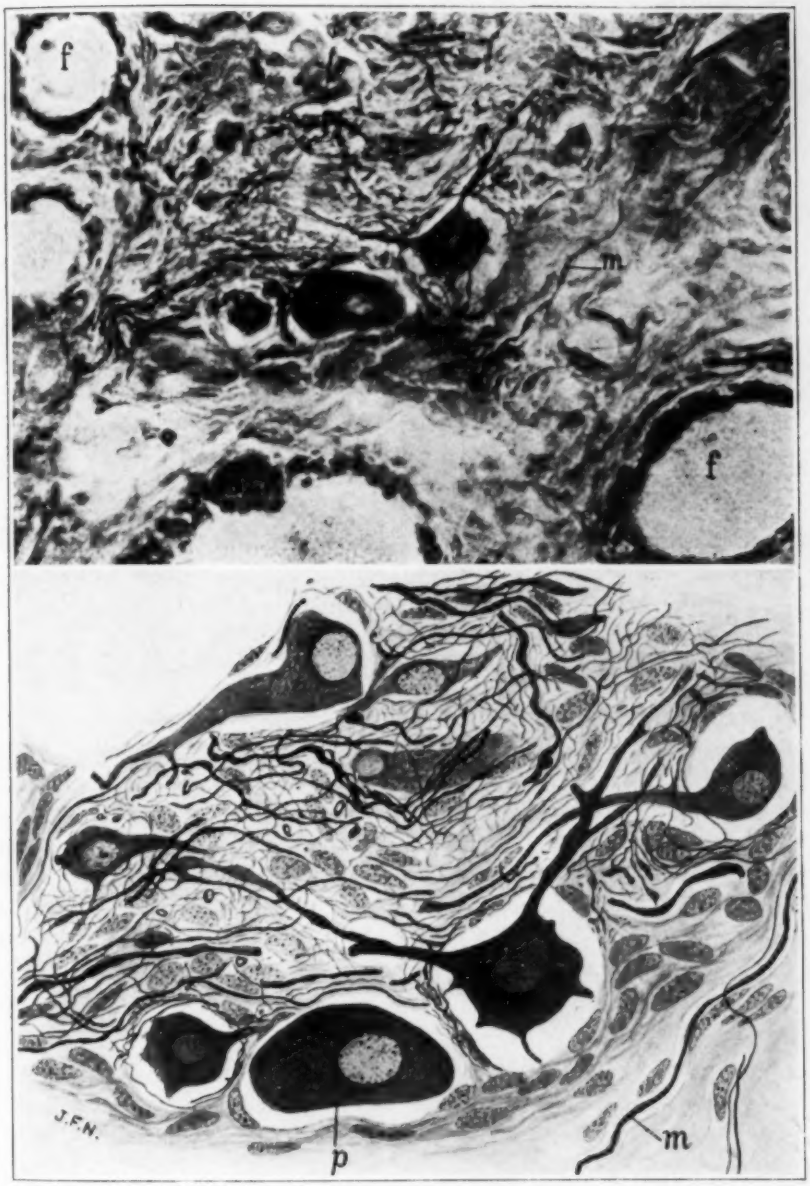

Fig. 3.—Photomicrograph and drawing of a large ganglion of the thyroid of a puppy, about 6 months old: *f*, follicles of the thyroid; *m*, myelinated fiber outside of the ganglion; *p*, polar view of a large neuron. Notice the elaborate plexus of fibrils within the ganglion, some of which end in rings. Alcohol-chloral hydrate fixation.

ficial reticulum). In older puppies, the neurofibrils are usually well impregnated in the cell body as well as in the dendrites (fig. 3).

In a few neurons, a thin prolongation of uniform diameter is seen arising from the cell body (figs. 1, 5 and 7, *a*). These prolongations are, in all probability, the axons of the cells. This belief is based on the fact that they do not give off collaterals within the ganglion, which is a well known characteristic of the axons of sympathetic ganglion cells.

The neurons of the ganglia of the thyroid are surrounded by a delicate, elaborate plexus of thin fibrils wrapped around the capsules. A few of these fibrils cross the capsules and are wound around the cell bodies of the neurons. In this respect, the ganglia of the thyroid resemble similar ganglia in other organs.

As already stated, there are in the ganglia of very young puppies small, round cells with faintly stained neurofibrillar network. In some of these elements the neurofibrils do not appear impregnated. Since the cells just mentioned are larger than the elements forming the capsules and the cells of the neurilemma, and, since in many instances, they appear surrounded by rudimentary capsules, they are regarded as neuroblasts that have not completed their evolution. In the ganglia of older puppies, such cells seem to be absent or are very scarce.

RELATION OF THE GANGLION CELLS TO THE NERVE FIBERS

One of the most important points in the interpretation of the innervation of the thyroid is the relation of the ganglion cells to the nerve fibers. Equally important is the final distribution of the axons of the neurons within the gland. The results thus far obtained in regard to the first point clearly indicate that, as in the case of other ganglia, certain nerve fibers enter into synaptic relations with the ganglion cells. The finer details of the synapse could not be worked out in the material available owing to the relatively small number of neurons and the difficulties encountered in their successful impregnation. Yet, the few cases observed furnish positive evidence of the existence of synapses similar to those present in other ganglia.

In my former contribution, I reported the presence of myelinated fibers in the thyroid of the dog and the guinea-pig. The existence of myelin sheaths was clearly demonstrated in osmicated sections. Myelinated fibers occur in all of the main branches of the nerve entering the thyroid along with the rami glandulares of the superior thyroid artery. A few fibers are quite thick, others are of medium and small caliber. While the presence of myelin sheaths is not a safe criterion of the origin and functional significance of the nerve fibers, other character-

istics led me to the view that at least the medium-sized and thin myelinated fibers are preganglionic fibers effecting connections with ganglion cells within the thyroid.

The use of the method of Cajal has further added to the knowledge concerning the distribution of the myelinated fibers in the thyroid. On the other hand, experimental evidence not yet published clearly indicates that most of the myelinated fibers are derived from the vagus, since they degenerate after section of the superior laryngeal nerve at its exit from the ganglion nodosum. The fibers under consideration seem to belong, therefore, to the bulbar outflow of the parasympathetic division of the autonomic nervous system.

While it is true that myelinated fibers in the gland are not numerous, their behavior in the ganglia assures a maximum of connections with the ganglionic neurons. These connections are established by means of pericellular baskets formed by collaterals and terminals of the fibers.

The most interesting feature in regard to the myelinated fibers in the thyroid is their tendency to form loops within the ganglia, thus coursing through the latter twice in opposite or nearly opposite directions. In other cases, the fibers instead of reentering the nerve from whence they came leave the ganglion through one of the efferent branches after forming a loop.

The peculiar behavior of the recurrent fibers is best seen in the smaller ganglia, since the latter are often included in one section. In larger ganglia, the course of a given fiber would have to be reconstructed from several sections. The two small ganglionic swellings seen in figure 5 (photomicrograph) were found ideal for the study of the behavior of the fibers under discussion. An enlarged drawing of ganglion *g* at the left of the photograph is given in figure 4, while a portion of the other ganglion has been represented in figure 5.

In the case represented in figure 4, two thick fibers (*a*, *b*), arriving at the ganglion by way of the afferent nerve are sharply bent near the point of emergence of one of the efferent nerves (*e*) which carries only unmyelinated fibers. One of the fibers (*b*) divides into two branches (*b'*, *b''*) within the ganglion, one of the branches (*b'*) being lost among the ganglion cells, while the other (*b''*) enters an efferent nerve (*e'*) which also carries a thick fiber. Fiber *a* recrosses the ganglion and enters the afferent nerve, passing once more through the ganglion represented in figure 5. Similar bending is seen in the case of two thinner fibers in figure 4.

An equally clear case of a recurrent fiber is seen in figure 5, *r*, but in this instance the loop lies outside of the ganglion. It will be noticed that the loop is in contact with terminal dendritic bulbs (*d*) from scattered neurons located outside of the ganglion. Although the

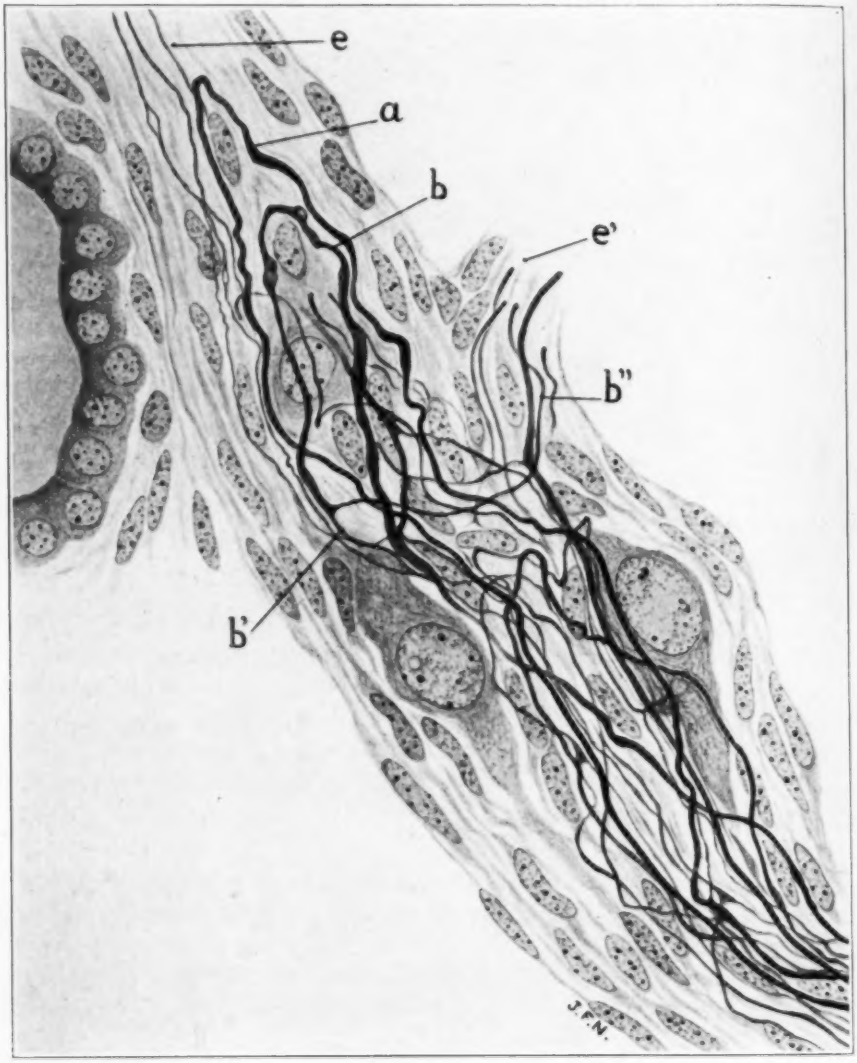

Fig. 4.—Recurrent nerve fibers in a small ganglion of a new-born puppy (labeled *g* in figure 5): *a*, *b*, two thick recurrent fibers; *b'*, *b"*, branches of bifurcation of fiber *b*; *c*, *c'*, efferent branches of the ganglion. Alcohol-ammonia fixation.

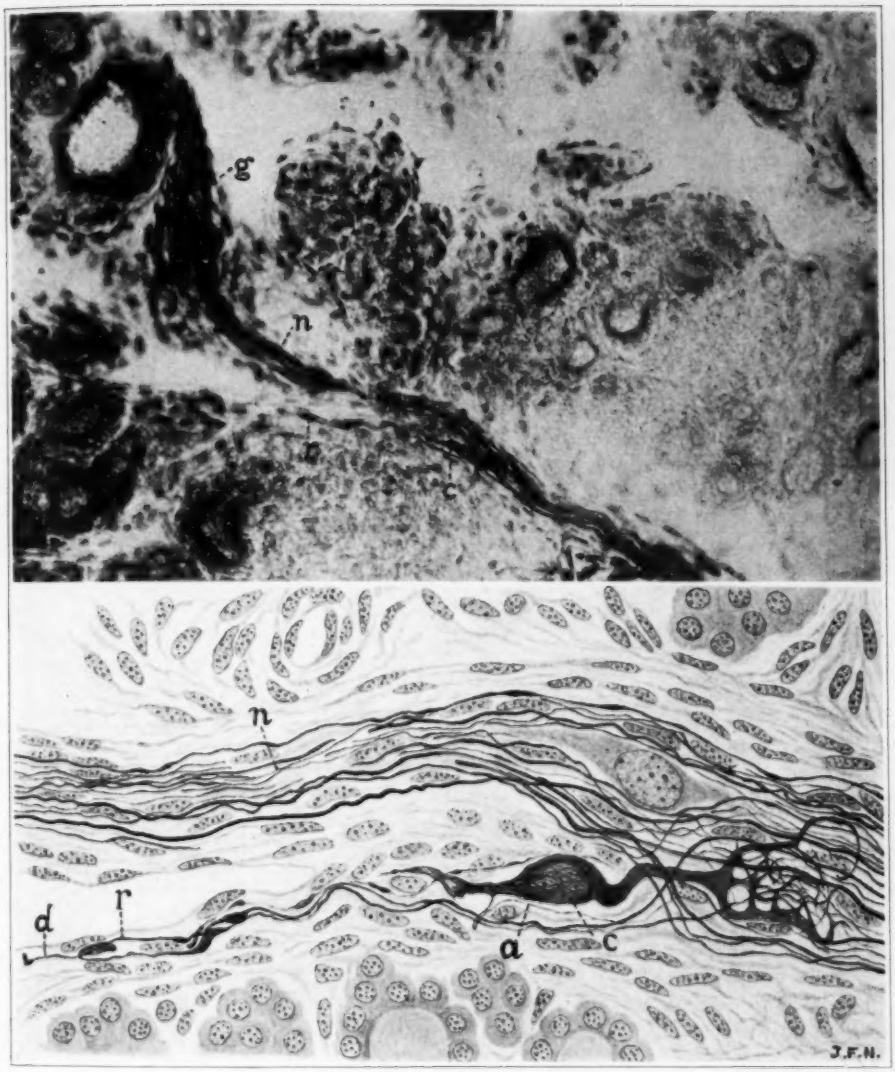

Fig. 5.—The upper figure is a photomicrograph of a nerve with two ganglionic swellings (ganglion *g* represented in the preceding figure). The lower figure is a drawing of the ganglionic swelling at the right, showing a well impregnated neuron, *c*; *a*, thin prolongation, probably the axon of the cell; *d*, dendritic bulb of a neuron located in the parenchyma; *n*, nerve; *r*, recurrent fiber outside of the ganglion. Alcohol-ammonia fixation.

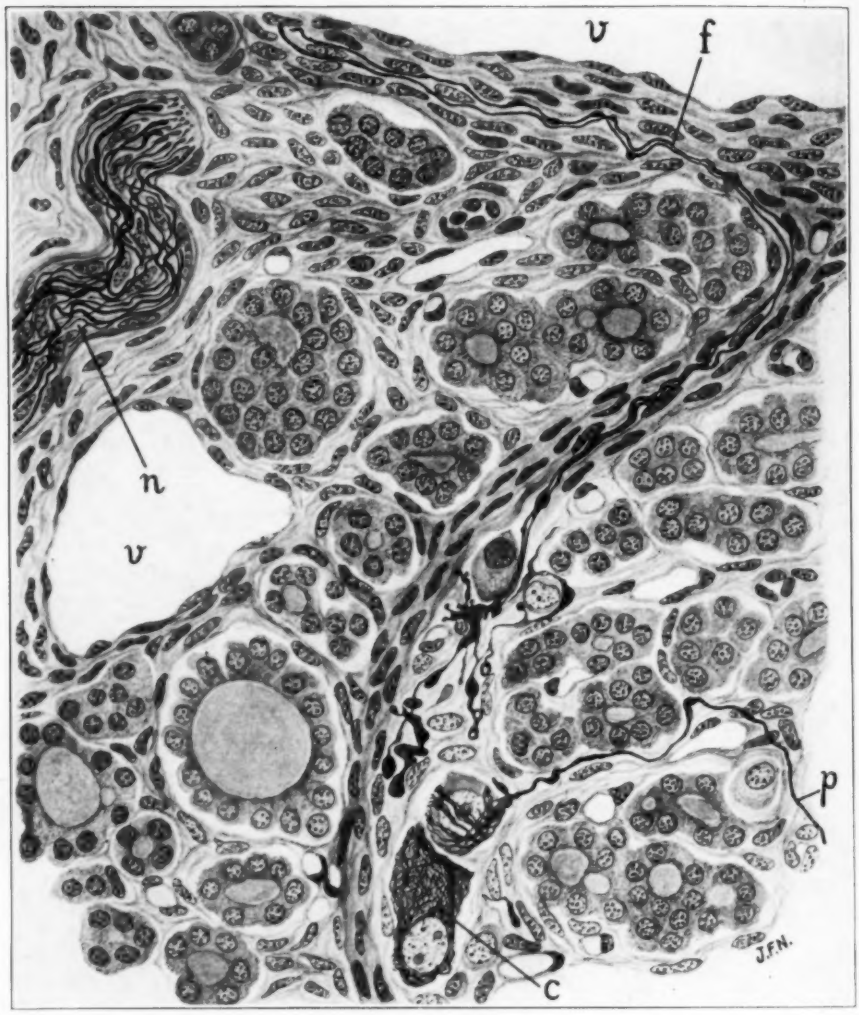

Fig. 6.—Tangential section of a ganglion independent from the nerve trunks in a new-born puppy: *c*, large neuron showing neurofibrillar network; *f*, two preganglionic fibers issued from the nerve *n*; *p*, preganglionic fiber ending as a basket on a neuron with faintly stained cytoplasm; *v*, lymph vessels. Alcohol-ammonia fixation. Section counterstained with indigo carmine.

loop possesses reticulated swellings, it does not seem likely that they are for the purpose of establishing synapse with the scattered neurons.

The presence of loops formed by recurrent fibers is particularly evident in those small ganglionic masses which represent the terminal ganglia of a chain extending along the main nerve trunks. The peculiar bending of the fibers suggests that their primary function is to effect multiple connections with the neurons in the ganglia. This supposition is strengthened by other facts. That some of the thick fibers in the nerves are preganglionic fibers is well illustrated in figure 6, which represents a tangential section of a ganglion independent from the nerve trunks. The ganglion in this instance appears embedded in the parenchyma, at some distance from a nerve (*n*). Two fibers (*f*) leave the nerve (their actual emergence is not seen in the section) and entering a septum of connective tissue they are seen to approach the ganglion, which they enter. Unfortunately, their terminations are not contained in the section copied; the irregular, varicose branches seen in the figure are the dendrites of the small neuron in the upper end of the ganglion. Another fiber (*p*) from an apparently different source is also seen coursing toward the ganglion, where one of its branches ends as a pericellular basket around a neuron with faintly stained cytoplasm, placed almost in contact with a larger cell with well stained neurofibrils (*c*). The cell represented in figure 7*A* was copied from a section of the same ganglion.

Another illustration of the fact that some of the thick nerve fibers effect connections with the neurons is seen in figure 1. A fiber (*p*), clearly seen in the photomicrograph, crosses the ganglion and ends as a basket around a deeply stained neuron. In this particular case the finer branches of the basket cannot be clearly distinguished from the coarse neurofibrils of the peripheral reticulum since the neurofibrillar framework appears deeply stained.

From these descriptions it seems clear that the neurons of the ganglia of the thyroid receive impulses through fibers that enter the gland along with other fibers ending on the vessels. They seem to establish synaptic relations with the cell bodies of the neurons (axosomatic synapses), but relations of contact with the dendrites (axodendritic synapses) may also occur, especially in those cases in which the dendrites of a neuron form pericellular baskets around the cell bodies of other neurons (fig. 7*A*). Dendritic arborizations wound around cells with pericellular baskets of axonic origin would, in fact, secure relations of contact for those cells that do not receive collaterals or terminals of nerve fibers.

In addition to the recurrent fibers, the ganglia may contain thick myelinated fibers that do not seem to effect connections with the gang-

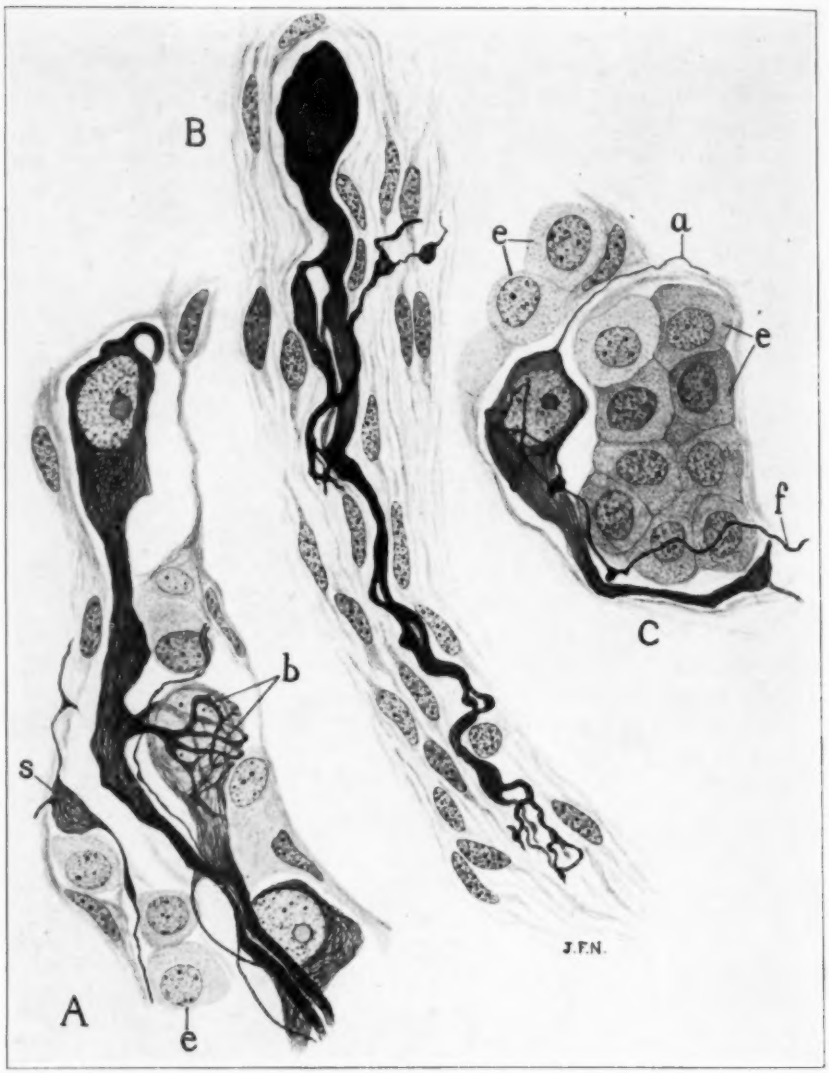

Fig. 7.—Sections from a new-born puppy. *A*, neuron with dendrites forming a pericellular basket (*b*) on the cell body of another neuron; *e*, epithelial (follicular) cells; *s*, reticulated swelling on a nerve fiber. *B*, a periarterial neuron embedded in the externa of a large arterial trunk. *C*, isolated neuron embedded in the parenchyma. *a*, thin prolongation, probably the axon; *e*, epithelial (follicular) cells; *f*, preganglionic fiber wound around the cell body of the neuron. Alcohol-ammonia fixation.

lion cells. In some cases, similar fibers are seen outside of the ganglia (fig. 3, *m*). The thick fibers under discussion are, in all probability, afferent or sensory fibers from the cerebrospinal ganglia.

SCATTERED GANGLION CELLS

In addition to the ganglia, there may be isolated ganglion cells in the stroma separating the follicles (interstitial neurons) or in the externa of the arteries (periarterial neurons). The nervous nature of these cells is well shown in sections stained with the method of Cajal since their neurofibrils are usually quite deeply stained.

The interstitial neurons have few, thick dendrites extending among the follicles. They end freely by means of reticulated swellings of variable size. In favorable cases, preganglionic fibers reaching the cell body, where they end in simple arborizations, can be clearly seen (fig. 7*C*). In some of these cells, a thin prolongation of uniform diameter (same figure, *a*) probably represents the neuraxon. Well developed capsules of connective tissue are absent around these cells. When present, the cells under discussion tend to appear scattered over certain areas of the thyroid, usually toward the center. The elements represented in figures 85 and 86 of my former paper probably belong to this type. For the most part they are cells of small or medium size receiving impulses from preganglionic fibers which follow a very erratic course after leaving the nerve trunks.

The periarterial neurons are rare. One of these cells has been represented in figure 87 of my former article. It was reported there that the dendrites of these cells are distributed over the walls of the arteries in which they occur, and are lost in the elaborate plexuses of the periarterial nerves, well impregnated in Golgi slides. These facts have been confirmed in the material prepared with the method of Cajal. Figure 7*B* represents a deeply stained neuron enclosed in the externa (or adventitia) of one of the larger arterial trunks. The cell has a monopolar aspect: the main dendritic stem soon divides into thick branches of irregular outline ending within the adventitia. The periarterial cells probably possess neuraxons, but I have not found any of these prolongations in my slides. These elements probably receive impulses from preganglionic fibers which may run in the arterial plexuses or may be derived from nerve bundles in the vicinity of the artery.

COMMENT

The descriptions in the preceding pages clearly indicate that the thyroid of the dog, investigated from the standpoint of its innervation by several authors (Anderson, Berkeley, Rhinehart, Popow), may possess typical ganglia embedded in the parenchyma. The same is probably true of other mammals, including man.

That no ganglia have ever been described in sections of the thyroid of the dog stained with routine methods is rather surprising since their neurons are quite large. But since the ganglia may be widely scattered, and are usually of small size, unless complete series of sections of whole thyroid lobes are examined, it is easy to miss them. In newborn or very young puppies the task is considerably simplified, especially when the neurofibrillar methods of staining are used. The latter stain the neurofibrils in the cell bodies and dendrites of the neurons, thus removing any possible doubt as to the nervous nature of these elements. It must be stated, however, that successful impregnation of small ganglia in glandular organs is usually difficult, the chances of success depending largely on the technical skill of the investigator.

The idea that the ganglion cells of the thyroid have entered the gland accidentally does not find support in the observed facts. The presence of fibers effecting connections with the neurons in the ganglia strongly indicates that the latter receive impulses from the central nervous system through preganglionic fibers. It is possible that some of the latter arise from the spinal cord and reach the thyroid after crossing the cervical sympathetic. However, the fact that the thyroid develops as a diverticulum of the floor of the embryonic pharynx suggests that the preganglionic fibers may come from the same source as many of the corresponding fibers supplying the ganglia of the alimentary tract (the descending colon excluded), namely, from the vagus. If such is the case, then the thyroid would also be supplied by the parasympathetic division of the autonomic nervous system.

The fact that some thyroids contain numerous neurons grouped into definite ganglia or appearing as elements scattered along the path of the nerves, and that in other glands neurons are very rare, suggests that their function is not primarily related to secretory phenomena in the follicular cells. In all probability they are concerned in the regulation of the circulation of the organ. In this regard it should be remembered that in many dogs there is no inferior thyroid artery. Even when present this vessel is much smaller than the superior thyroid artery. The presence of a double blood supply in some thyroids may necessitate the existence of regulatory nervous mechanisms to facilitate the distribution of blood flowing in nearly opposite directions through vessels of unequal size, and arising from arteries of large caliber.

EXPERIMENTAL POLIOMYELITIS

HISTOLOGY OF THE PERSISTENT LESIONS OF THE CENTRAL NERVOUS SYSTEM *

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NEW YORK

The histopathology of acute poliomyelitis in both man and monkey has been repeatedly and thoroughly discussed, whereas the stage of recovery and repair has received little attention in the literature. Although residual lesions in the central nervous system of human cases of long standing have been described, the necropsy material has been scarce, since the death of patients during that period depended not on the poliomyelitic infection but on intercurrent illness and accident. Many years of investigations on the monkey have shown a close correlation between the clinical manifestations of the experimental disease in these animals and with those in man, but owing to the severity of the infection, death tended to take place in the acute stages or before recovery had proceeded very far.

It was possible, in this laboratory, to keep fifteen *Macacus rhesus* monkeys alive for periods varying from 19 to 309 days after the onset of symptoms. Careful nursing during the prostrate paralytic period was often necessary to maintain nutrition and to avoid decubitus, and while some animals died despite these measures, others regained full functional activity of all four extremities. A study was therefore made of all the variations of disease and recovery of the central nervous system in order to determine the persistence of active inflammatory lesions and the rate of progressive repair, in the thought that such information might be of value in its application to human poliomyelitis from the point of view of prognosis and treatment.

REVIEW OF THE LITERATURE

The typical pathologic changes in cases of acute poliomyelitis have been described by many authors, notably by Medin,[1] Wickman,[2] Zappert, von Wiesner and Leiner,[3] Römer,[4] Flexner and Lewis,[5] Land-

* Submitted for publication, Oct. 16, 1930.

* From the Rockefeller Institute, New York.

1. Medin, O.: Hygiea **52**:657, 1890.

2. Wickman, I.: Die akute Poliomyelitis beziehungsweise Heine-Medinsche Krankheit, Berlin, Julius Springer, 1911.

3. Zappert, V.; von Wiesner, R., and Leiner, K.: Studien über die Heine-Medinsche Krankheit, Vienna, Franz Deuticke, 1911.

4. Römer, P.: Die epidemische Kinderlaehmung, Berlin, Julius Springer, 1911.

5. Flexner, S., and Lewis, P. A.: J. Exper. Med. **12**:227, 1910.

steiner [6] and more recently by Hurst.[7] Essentially, these investigators agree regarding the histopathology of the disease, although there have been differences in the interpretation of the origin and significance of the lesions themselves.

The chronic stages, on the other hand, have received little attention. Schwalbe [8] summarized the clinical and pathologic reports of fourteen cases of chronic poliomyelitis, collected from the literature prior to 1902, which came to autopsy at periods varying from five months to sixty-five years after the onset of the paralysis. From his outline it appears that scattered lesions in the cords were present that had not given rise to clinical signs, that cicatrization was noted as early as the fifth month, that perivascular lesions were found in two cases of five months' and two years' duration respectively, and that obliteration and degeneration of the nerve cells were universally present in focal areas.

Schwalbe also reported a case of approximately four months' standing which he considered characteristic of the "reparative" phase. The patient had suffered from acute poliomyelitis before death occurred from an intercurrent disease. Clinically, only the left leg gave evidence of involvement, but the damaged area penetrated higher and lower levels than had been suspected, while a focus of degeneration which had given no symptoms was found in the right lumbar cord. Grossly there was no shrinkage of the anterior horns characteristic of scar formation, but on section the gray matter was found to retract from the cut surface. On microscopic examination, the areas of destruction were seen to be localized in the central portion of the anterior horn and showed a tendency to spread upward and inward rather than laterally. The nerve cells about the outer border showed the better state of preservation where the entire anterior horn was not involved. Schwalbe remarked on the patchiness and inconsistency of the lesions at adjacent levels in the cord, and described changes in the nerve cells of four types: (1) pale cells with visible nuclei, faint processes and loss of Nissl substance; (2) shrunken, darkly staining cells, which occasionally contained granular cytoplasm, but in which the nuclei and processes were no longer discernible; (3) cells in all of the stages between those described and normal cells (these were usually seen at the borders of the lesion) and (4) "calcified" cells. There was found to be no direct relation between destruction of the nerve cells and the perivascular reaction since vascular adventitial spaces filled with fat and

6. Landsteiner, K., in Kolle, W.; Kraus, R., and Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, Jena, Gustav Fischer, 1929, vol. 8, p. 38.

7. Hurst, E. W.: J. Path. & Bact. **32**:457, 1929.

8. Schwalbe, E.: Beitr. z. path. Anat. u. z. allg. Path. **32**:485, 1902.

fat containing cells were seen in one posterior horn and in the anterior horns above and below the levels at which other abnormalities were demonstrable. Hyperemia and proliferation of vessels were noted. The perivascular infiltrate was described as consisting of cells containing fat and round cells. The latter were also observed in the gray matter about the areas of destruction, together with clumped "Fettkoernchenzellen." Fat was seen lying in the "spaces" around the nerve cells and about the nerve fibers in the anterior roots, anterior columns and the gray commissure.

No disturbances of the fiber tracts were noted, but there was a loss of neurofibrils in the anterior roots and in the areas of destruction in the gray matter, in which Schwalbe noted a fine glial network which suggested a condition similar to that of "gliosis." As there was no increase in glia nuclei, and as fat-containing cells were often seen, he concluded that in all probability there was no true glial proliferation and that the scar formation of the late "residual" stage had not set in.

A number of cases of chronic human poliomyelitis were reported between 1902 and 1911, but after the successful inoculation of monkeys with the virus, in 1909, by Landsteiner and Popper,[9] far more attention was given to the acute phases of the disease. In only a few laboratories were pathologic studies undertaken on the recuperative changes.

Levaditi and Stanesco (1910) [10] discussed the lesions in three monkeys that had survived the onset of the disease for periods of twenty-one, twenty-nine and sixty-seven days. Two of these suffered from a paraplegia, one from monoplegia. Only the third showed mononuclear and polymorphonuclear cells in the cortical meninges together with cerebral perivascular infiltration. In the brain stem, active inflammatory areas were found. In the cervical and thoracic regions of the cord no pathologic signs were present, but the lumbar segments showed signs of a less active process, in which practically no nerve cells remained in the anterior horns, perivascular lesions persisted, and the tissues were infiltrated with mononuclear cells. It was thought that these lesions corresponded to the clinical observations in that only unilateral damage was present in the anterior horn in the case with monoplegia, while peripheral nerve degeneration corresponded with the affected spinal levels as did the atrophic muscles supplied by them. In contradistinction to acute poliomyelitis, no lesions of the meninges or vessels of the white matter were seen in the cords, while in the gray matter there were no polymorphonuclear cells, and "chronic inflam-

9. Landsteiner, K., and Popper, E.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **2**:377, 1909.

10. Levaditi, C., and Stanesco, V.: Compt. rend. Soc. de biol. **68**:664, 1910.

mation" was characterized by mononuclear infiltrates about the vessels and in the tissues. The posterior horns were spared.

The presence of acute lesions in the brain stem was regarded as a sign of a recurrence in that location after the process of the disease in the lumbar area had passed the phase of active destruction. This condition was thought to be due to the slow development of an immunity to the infection. The predilection of the virus for the lumbar cord, regardless of the route of inoculation, was also pointed out.

In 1911, Römer [4] described the stage of repair in a *Macacus rhesus* monkey that showed a paraplegia persisting until death thirty-six days after the onset of the disease. The brain was not examined. Although no lesions were found in the cervical and dorsal spinal cord, bilateral involvement of the anterior horns of the lumbar region was observed, characterized by widespread destruction without signs of the formation of scar tissue or vascular proliferation. The fibrous structure was described as "porous," so that only a fine fibrillar network, studded with small clumps of round cells, interlaced the meshes. Perivascular infiltration was present, and nerve cells were almost completely absent. Glial proliferation and Fettkoernchenzellen were remarked as characteristic of the process of repair. Four other animals were also reported, which recovered completely without traces of residual paralysis, and in which histologic examination revealed no lesions whatever in the nervous system. A fifth monkey had made a distinctly progressive recovery following paraplegia and paralysis of the upper extremities, only to relapse on the twentieth day after the onset of the symptoms, so that quadriplegia was followed by death two days later. In this case the spinal cord showed typical lesions of acute poliomyelitis.

Römer's description of the residual stage of the human disease agreed with that of Müller (1911) [11] who stated that a thick scar was ultimately produced in the damaged areas by glial proliferation after the elimination of detritus by "Koernchenzellen." A cross-section of the cord showed the anterior horns to be grossly shrunken and depressed. Microscopically, the neighboring tracts and anterior roots were found to be atrophic. Degeneration of the other fiber tracts was also mentioned together with secondary changes in the central convolutions of the brain in longstanding cases in which atrophy of the extremities had persisted.

In the more recent literature, there have been remarkably few references to the pathology of chronic poliomyelitis. Hurst [7] reported one case in a *M. rhesus* monkey that was intracerebrally infected

11. Müller, E.: Handb. d. inn. Med. **1**:840, 1911.

with the "Ay" virus, and in which acute symptoms developed: double ptosis, paralysis of the right arm and paresis of both legs. The animal showed partial recovery of function in the affected limbs, and was killed on the thirty-fifth day after the onset. On pathologic examination, no gross abnormalities were noted in the central nervous system. Microscopically, a marked loss of neurons was evident at the affected levels, but the remaining nerve cells were normal in appearance. There was no perivascular or meningeal reaction. In the involved areas, there was a definite increase in neuroglia cells which were large and had many processes, but no definite fibril formation was observed. The microglia also showed proliferation, representing all of the forms from normal cells to compound granular corpuscles laden with fat. The latter were seen in the greatest number lying about the capillaries and small vessels, or, in the case of the granular corpuscles, in the perivascular spaces. Lipoid staining material was also found in the tissues of the anterior horns. The myelin sheaths were reduced in number, ballooned and irregular in their staining reaction, while degeneration was seen in the medullated fibers leading to the anterior roots, where no degeneration of the fiber tracts was observed. The median nerves showed advanced myelin destruction. Other regions of the central nervous system proved to be entirely normal.

EXPERIMENTAL WORK

Fifteen *Macacus rhesus* monkeys, previously used for various experiments on poliomyelitis in this laboratory, had been carefully nursed through the acute phases of the disease to partial or complete stages of functional recovery. They had been infected by intracerebral inoculation, by nasal instillations or by injections of virulent material into the lumbar or cisternal theca. These procedures have been described elsewhere [12] and will not be discussed here. The M.A. virus, referred to by Hurst [7] as "A.M.," was a weak strain, as were the Ay and Mt.S. viruses. The first of these was obtained from the lumbar cord in a human case of poliomyelitis, in 1909, which at that time was passed to monkeys by Flexner and Lewis; [13] the second was a human strain passed to monkeys by Aycock and Kagan,[14] whereas, the third was a pooled virus from parts of the central nervous system of three patients with acute poliomyelitis, sent to the Rockefeller Institute from the Mount Sinai Hospital in New York. In general, the animals showed a tendency toward more complete functional rehabilitation after infection with these three viruses than after inoculation with the strong PMV [15] strain, designated as

12. Rhoads, C. P.: J. Exper. Med. **53**:115, 123 and 137 (Jan.) 1931; **53**:399 (March) 1931.

13. Flexner, S., and Lewis, P. A.: The Transmission of Acute Poliomyelitis to Monkeys, J. A. M. A. **53**:1639 (Nov. 13) 1909.

14. Aycock, W. L., and Kagan, J. R.: J. Immunol. **14**:85, 1927.

15. PMV is a pooled monkey virus consisting of a mixture of the M.A. and K strains. The latter was derived from a human spinal cord in 1909. Flexner, S., and Lewis, P. A.: The Transmission of Poliomyelitis to Monkeys, J. A. M. A. **53**:1913 (Dec. 4) 1909.

TABLE 1.—*Protocols of Monkeys with Poliomyelitis*

No.	Inoculation: Date	Route	Dose, Cc.	Virus	Clinical Course	Days
1	4/13/29	Cistern	0.005	PMV 5% F.F.*	4/28/29, tremor, ataxia; 4/29/29, paralysis of shoulder girdles and vocal staccato; from 4/30/29 prostrate, to 5/15/29, slowly progressive weakness; 5/16/29, found dead	19
2	12/ 3/28	Cerebral	1.0	Mt. S. 10% F.B.†	From 12/14/28 to 12/26/28, tremor, slight ataxia and excitement; 12/26/28, paralysis of the right shoulder girdle; 12/27/28, paralysis of the left shoulder girdle; 12/28/28, paresis of both legs and generalized weakness; 12/29/28, paralysis of the right arm and progressive weakness; 12/31/28, more active, with general condition improved; 1/2/29, further improvement and some functional recovery of the muscles; 1/11/29, etherized	29
3	4/15/29	Cistern	0.01	PMV 5% F.F.	4/19/29, ataxic, slow; 4/20/29, asymptomatic; 4/25/29, generalized convulsion; 4/27/29, paralysis of the right arm and tremor; 4/28/29, ataxia, paralysis of the left arm and paresis of both legs; 4/29/29, prostrate; from 4/30/29 to 5/28/29, prostrate, bright, slight movement of the left arm and head; able to raise head and shoulders and to pull itself about in the cage; etherized	40
4	10/1/29	Cerebral	0.02	PMV 5% F.F.	10/20/29, right facial paralysis and bilateral paresis of the shoulder girdle, excitement, tremor, ataxia; 10/11/29, paralysis of both shoulder girdles, progressive weakness; 10/12/29, paresis of the legs, able to sit up; 10/13/29, paralysis of the legs; unable to sit up, but crawls about; from 10/16/29 to 11/19/29, brighter; able to move head and shoulders; finally able to move arms and pull itself about in the cage; considerable improvement; etherized	41
5	From 10/17/29 to 10/19/29	Nasal	3 in 3 days	PMV 10% G‡	10/26/29, paralysis of the right leg and paresis of the shoulder girdles; tremor and ataxia; from 10/27/29 to 12/11/29, prostrate but bright; slight recovery of function; marked atrophy and contractures; etherized	47
6	From 10/17/29 to 10/19/29	Nasal	3 in 3 days	PMV 10% G.	10/26/29, excitement; 10/27/29, paralysis of both legs, staccato voice, tremor and ataxia; from 10/28/29 to 12/11/29, prostrate but bright; quadriplegia except for paresis of right shoulder girdle; recovery very slight; marked atrophy and contractures of all the extremities; etherized	47
7	3/ 5/29	Cerebral	0.5	PMV 5% F.B.	3/11/29, paresis of both shoulder girdles, excitement, tremor and ataxia; from 3/12/29 to 4/26/29, prostrate but bright; gradual recovery; able to move head, shoulders and trunk; refused food; 4/27/29, found dead; postmortem examination showed severe anemia	48
8	From 9/20/29 to 9/23/29	Nasal	3 in 3 days	PMV 10% G.	9/29/29, excitement, tremor and ataxia; 9/30/29, paralysis of both shoulder girdles and double ptosis; 10/1/29, paresis of the left arm and both legs; 10/2/29, prostrate but bright; from 10/4/29 to 11/19/29, slight improvement; partial functional recovery of all four extremities; etherized	52

* F.F. = fresh brain filtrate.
† F.B. = fresh brain suspension.
‡ G. = glycerolated brain suspension.

TABLE 1.—*Protocols of Monkeys with Poliomyelitis—Continued*

No.	Inoculation				Clinical Course	Days
	Date	Route	Dose, Cc.	Virus		
9	5/31/28	Cerebral	0.2	Ay. 5% F.B.	6/6/28, left facial paralysis; slight ptosis, excitement and head tremor; 6/7/28, paralysis of shoulder girdles and back, ataxia; 6/8/28, paralysis of both legs; 6/9/28, prostrate but bright; 7/21/28, very slight recovery; able to lift head; all limbs atrophic and spastic; edema and decubitus; 8/3/28, dying; etherized	59
10	2/ 5/29	Cerebral	0.01	PMV 5% F.F.	2/15/29, paralysis of the left shoulder girdle, excitement, tremor and ataxia; 2/16/29, paralysis of both arms and shoulder girdles, paresis of the left leg and back; 2/17/29, prostrate but bright; from 2/20/29 to 4/26/29, able to raise head but generally weaker; slow improvement, able to move head, neck and arms and to pull itself about in cage; poor nutrition; 4/27/29, found dead; postmortem examination revealed severe anemia	72
11	10/ 3/28	Cerebral Peritoneal	1.00 15.00	Mt. S. 10% F.B.	10/12/28, paresis of the left shoulder girdle and both legs, diarrhea; 10/13/28, paresis of the right shoulder girdle and back; 10/14/28, paralysis of the left shoulder girdle and legs, diarrhea; 10/15/28, paralysis of the left arm, right shoulder girdle and both legs, tremor; from 10/16/28 to 10/30/28, slightly more active; almost complete recovery of function despite residual atrophy of all four extremities; 1/3/29, emaciated; severe diarrhea; etherized	84
12	5/16/28	Cerebral	0.2	Ay. 5% F.F.	5/27/28, excitement, tremor and ataxia; from 5/28/28 to 5/31/28, paralysis of both arms and paresis of the back; prostrate but bright; from 6/1/28 to 1/23/29, prostrate and weak; complete functional recovery despite residual atrophy; etherized	242
13	5/ 3/28	Cerebral	0.1	Ay. 5% F.F.	5/10/28, left facial paralysis, vocal staccato and ataxia; 5/11/28, paralysis of shoulder girdles, paresis of the legs and back, tremor; 5/12/28, paralysis of the left arm and the right leg; from 5/13/28 to 1/23/29, paralysis of left leg; complete functional recovery despite residual atrophy; etherized	259
14	4/23/28	Cerebral	0.3	Ay. 5% F.F.	5/2/28, excitement; 5/3/28, paresis of the left leg, tremor and ataxia; 5/4/28, paresis of lumbar spine; from 5/5/28 to 5/31/28, paresis of the right leg and the right shoulder girdle; almost complete functional recovery despite residual atrophy; 1/23/29, etherized	267
15	3/ 3/28	Cerebral	0.3	M. A. 5% F.B.	3/21/28, paresis of the right shoulder girdle, excitement and ataxia; 3/22/28, paralysis of the right shoulder girdle and paresis of the left leg, tremor; 3/23/28, paresis of lumbar back; 3/24/28, paresis of the right arm; 1/23/29, complete functional recovery despite residual atrophy; etherized	309

"FI" by Hurst, which was followed by subacute or chronic poliomyelitis, although it is probable that the animals in cases 3, 4 and 8 might have rallied further had the period of convalescence been prolonged.

The clinical data are incomplete from the neurologic point of view, owing to the fact that the present study was undertaken after the completion of the experiments in which the animals were originally used, and after the majority of them had been killed, so that it was impossible to correlate the pathology of the central nervous system with the symptomatology. In the protocols in table 1 the term "prostrate," unless otherwise modified, signifies a condition in which there was partial or complete quadriplegia together with paralysis of the bladder. The animals were generally able to move their heads, and mastication and deglutition showed no obvious disturbances. Facial paralyses were usually early and transitory. The condition referred to as "complete functional recovery despite residual atrophy" was one in which the monkeys climbed about freely, although there was limitation of motion of the hind legs, and, to a lesser extent, of the upper extremities, owing to contractures and atrophy of various groups of muscles.

It will be seen from these protocols that case 1 survived for nineteen days but ran a progressively downhill course comparable with that of the severe acute cases of shorter duration. It has been included in this series as illustrative of the transition between the acute condition described by Hurst and the later group dealt with here.

METHOD

Autopsy was performed on the animals as soon as possible after death, or immediately following etherization and exsanguination. The central nervous systems were fixed and stained as follows:

Formaldehyde Fixation (10 per cent).—Frozen sections were stained for fat by Fettpenceau and hematoxylin, and Fettpenceau and silver impregnation; for macroglia, by Cajal's gold sublimate impregnation; for microglia and oligodendroglia, by Penfield's combined method,[16] and for neurofibrils, by Bielschowsky's method and Cajal's silver impregnation.[17]

In the last named method, the sections were cut at 25 microns, received in distilled water and washed well. Five or six sections were then placed in 10 cc. of a 2 per cent silver nitrate solution to which 6 drops of pyridine had been added, and warmed over an alcohol flame for from thirty minutes to three hours, depending on the completeness of impregnation at various intervals of time. The amber brown sections were then dipped in 95 per cent alcohol and transferred to Cajal's reducer for two minutes (hydroquinone, 0.2 cc.; formaldehyde solution [Merck], 30 cc., and distilled water, 80 cc.). After thoroughly washing the sections in distilled water, they were fixed in sodium hyposulphite, dehydrated and mounted in Canada balsam.

This method was found to be simpler than the Bielschowsky impregnation, but consistently good results were not obtained by either technic. There were such marked variations, even in the normal control animals, that when the sections showed questionable pathologic changes with the routine stains, these were disregarded in the presence of an intact fibrillar network, while the converse situation

16. Penfield, W., and Cone, W.: Neuroglia and Microglia (The Metallic Methods), in McClung, C. E.: Handbook of Microscopic Technique, New York, Paul B. Hoeber, 1929.

17. Ramon Cajal, S.: Trav. du lab. de recherches biol. de l'Univ. de Madrid **22**:157, 1924.

was considered significant only when the unaffected cells gave evidence of complete impregnation. Sufficiently good preparations were made in some cases to permit a study of the various phases of neurofibrillar degeneration.

Paraffin sections were stained for cellular structure with hematoxylin and eosin; celloidin sections for cellular structure with hematoxylin and eosin, and for nerve fibers and myelin by the Kulschitsky-Weigert method.

Zenker Fixation.—Paraffin sections were stained for cellular structure with eosin-methylene blue by Mallory's method, substituting phloxine for eosin, and for fibrous structure with phosphotungstic acid and with aniline blue by Mallory's methods.

Alcohol Fixation (95 per cent).—Celloidin sections were stained for cellular structure with cresylecht violet (the results obtained with this stain were not entirely satisfactory).

Formaldehyde-Ammonium-Bromide Fixation (Cajal).—Frozen sections were stained for microglia and oligodendroglia by an unpublished modification of Hortega's silver carbonate method by Hortega.[18] This method was found to give consistently good results and to impregnate the oligodendroglia cells more satisfactorily than Penfield's combined method. Counterstains for fat (Fettpenceau) were made which clearly showed its intracellular and extracellular distribution. The nerve cells were in many cases weakly impregnated with silver, which facilitated the study of their relationship to the glia cells.

The blocks were removed from the fixative between the sixth and the eighth day and were heated to from 45 to 50 C. in formaldehyde-ammonium-bromide for from five to ten minutes. After cooling and rinsing in distilled water, frozen sections were cut at 15 microns. These were received in distilled water and immediately transferred to strong ammonia where they were allowed to remain, in a dark bottle, for at least one hour. One or two sections were washed rapidly in distilled water, placed in a small covered dish of Penfield's strong silver solution [16] for from two to five minutes, and transferred to 1 per cent formaldehyde solution where they became a deep, uniform brown. After washing in distilled water, the sections were toned in cold yellow gold chloride (1:500), fixed in 5 per cent sodium hyposulphite, dehydrated and mounted in Canada balsam.

Macroglia were stained according to Cajal's gold sublimate method, after fixation in formaldehyde-ammonium-bromide.

Penfield's modification [16] was not used, as it was found that satisfactory results could be obtained with sections treated in the same way as in the modified silver carbonate method already described. After cutting the sections, those to be impregnated with gold were placed in weak ammonia over night, after which the same technic was used as with the formaldehyde-fixed material. In this way the astrocytes, microglia and oligodendroglia could be studied in sections cut from the same block.

In some cases the whole nervous system had not been fixed, while in many others all the material had been fixed in formaldehyde. Only two monkeys were killed after the present study was undertaken, and on these all the staining methods described were used throughout the entire nervous system. In other instances the technic was limited by the original fixation. Four cases were available for complete investigation on blocks fixed in formaldehyde-ammonium-bromide, although gold sublimate and Penfield's combined impregnations [16] were made on several spinal cords which had been hardened in formaldehyde.

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18. Personal communication from Dr. Lawrence Kubie.

HISTOLOGIC OBSERVATIONS

The histopathology of acute poliomyelitis in *Macacus rhesus* monkeys has been recently restudied by Hurst [7] who grouped his observations under the headings of pial infiltration, perivascular and extra-adventitial infiltration, diffuse and focal tissue infiltration, and nerve cell destruction. These lesions were discussed in respect to their distribution in the spinal cord, medulla and pons, midbrain, basal ganglia, cortex, cerebellum and other regions. This classification has been followed as closely as possible in order to facilitate comparison between the acute and chronic or recovered cases. The examination of the spinal cord has been subdivided into the lumbar, thoracic and cervical regions, and an attempt as been made to deal somewhat more specifically with the cortical lesions. No detailed description of the nuclei of the cranial nerves has been undertaken, since the clinical data were too incomplete to warrant an attempt at correlation with the pathologic observations.

It was possible to study the spinal cords of fifteen monkeys, the medullas of fourteen, the midbrains of eight, the basal ganglia of fifteen, the cortices of nine, the cerebella of nine and the intervertebral ganglia of nine, and to compare them with normal controls and with material from monkeys killed during the acute stages of poliomyelitis. In some instances only single sections through each area were available, and as the lesions are notably patchy in distribution, this report on the pathologic observations is in certain respects incomplete. Nevertheless, the material at hand presented a consistent picture, and suggested certain conclusions.

SPINAL CORD

No matter what the route of infection, it was found that with the exception of one case, the lumbar cord was most severely damaged and showed the greatest degree of active inflammation. The thoracic region was not spared to any appreciable extent, and examination of several segments showed a patchy, although fairly consistent, transition between the conditions present in the lumbar and cervical cords. The latter tended to show an arrested or reparative picture in the cases of long standing.

Pial Infiltration.—While Hurst [7] found a marked generalized meningeal reaction scattered over various levels and surfaces of the spinal cord at the height of the disease process, he made the statement that "until a fairly late stage pial infiltration is insignificant and confined to a light excess of cells in the deeper part of the opening of the anterior fissure, or around the vessels of this region, to the entry zone of the posterior nerve roots, or to the meninges over the posterior septum." It is interesting to note that this distribution of lesions at

the onset corresponds with that of the later period in those instances in which any meningeal reaction was discernible. Although the monkey in case 1 survived for nineteen days, the histologic picture here and elsewhere was entirely comparable with those in the severe acute cases of shorter duration. The infiltrate was found to be more widespread and to contain polymorphonuclear cells which were found in only one other monkey (case 13), in which they were very scanty and the pial reaction was focal and slight. In all other instances, the cells consisted of lymphocytic and mononuclear types and were few in number. In the majority of cases there was no pial reaction whatever, so that in general meningitis may be said to have been insignificant or absent.

Perivascular Infiltration.—The perivascular lesions of the group surviving from 41 to 84 days were far more marked and intense than those which were found in the cords of monkeys killed during the acute stage of the disease. According to Hurst, these infiltrates were most commonly localized about the large vessels in the neighborhood of the central canal, about the smaller vessels of the anterior and posterior horns, and about the vessels radiating through the white matter to the anterior fissure and to the periphery. In our series, on the other hand, lesions of this type were most extensive in the anterior horns and about the vessels leading to and from the anterior fissure, while the smaller vessels of the posterior horns were less often and less seriously affected. The central zone usually remained uninvolved, unless a large lesion of the proximal portion of the anterior horn encroached on it. Radial lesions occurred in four or five cases, but consisted of only a single layer of cells in the perivascular space, except in case 4, in which the vessels were surrounded by a broad cellular sleeve.

In the anterior horns, large areas were frequently found in which the nerve cells had been destroyed, the architecture of the ground substance had been partly or totally obliterated, and perivascular infiltration and capillary proliferation were abundant (fig. 1).

The infiltrate varied in magnitude from a few cells in the Robin-Virchow space to a wide perivascular cuff, and at times extended beyond the adventitial space into the surrounding tissues. Throughout, the number of lymphocytes predominated over the mononuclear cells. Hurst estimated that 10 per cent of the perivascular cells in the acute stages of the disease were polymorphonuclear leukocytes. In the present series of chronic cases only a few cells of this type were observed in cases 1, 4, 5, 6, 7, 11 and 13. Specific stains were not made for plasma cells, but none were identified definitely in the routine preparations.

Tissue Infiltration.—Focal and diffuse infiltrations were more prominent in the earlier cases of this series than in the acute stage of polio-

myelitis. Particularly in the areas of parenchymatous destruction of the anterior horns, many cells were seen lying about the periphery of the Robin-Virchow spaces, about the proliferating small vessels and about degenerating nerve cells, while independent cell masses were also common. The density of the infiltrate bore a direct relation to the extent of damage done to the tissues, so that lesions of decreasing severity were found in Clarke's column and in the posterior horns, in which they were often slight and focal in comparison with the dense generalized

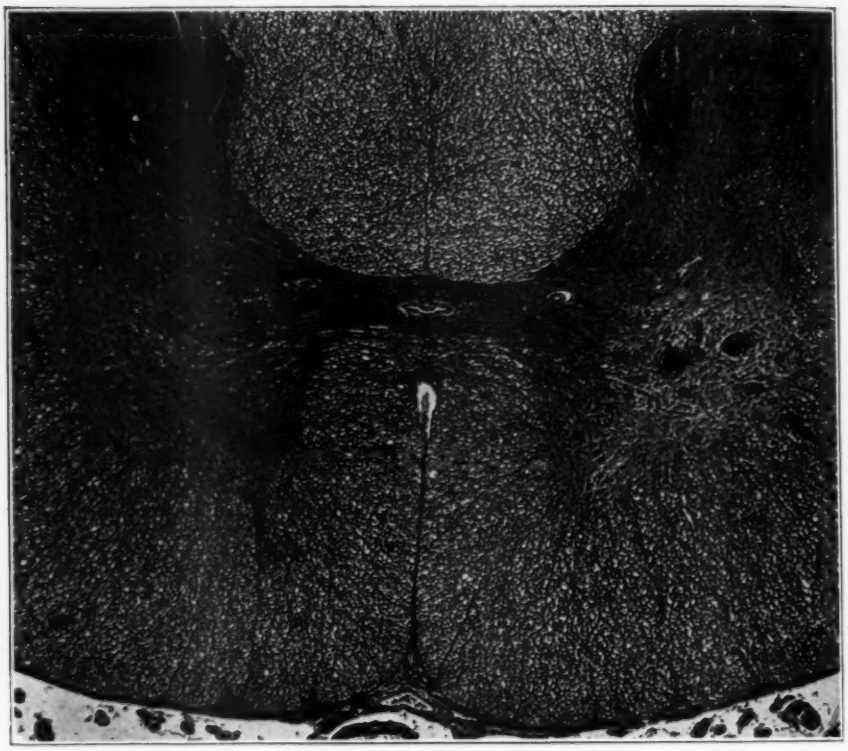

Fig. 1 (case 5).—Section of the lumbar cord showing an area of destruction in one anterior horn. Phosphotungstic acid and hematoxylin; × 33.

infiltration of the ventral portion of the cord. In contradistinction to Hurst's observations in acute poliomyelitis, the numerical cellular increase about the central canal was minimal, and the canal itself was invariably empty. In general, it may be said of the gray matter that tissue infiltration varied directly with destruction of the neurons and inversely with the process of repair. Small focal lesions were also seen in the white matter together with a mild diffuse infiltration.

The cells taking part in this process were chiefly mononuclear, although a few polymorphonuclear leukocytes were found in cases 3, 5, 6 and 10, while case 1 again approximated the picture of acute poliomyelitis. Lymphocytes were plentiful in the more recent cases of the group, but rarer in those of long standing and in the absence of an

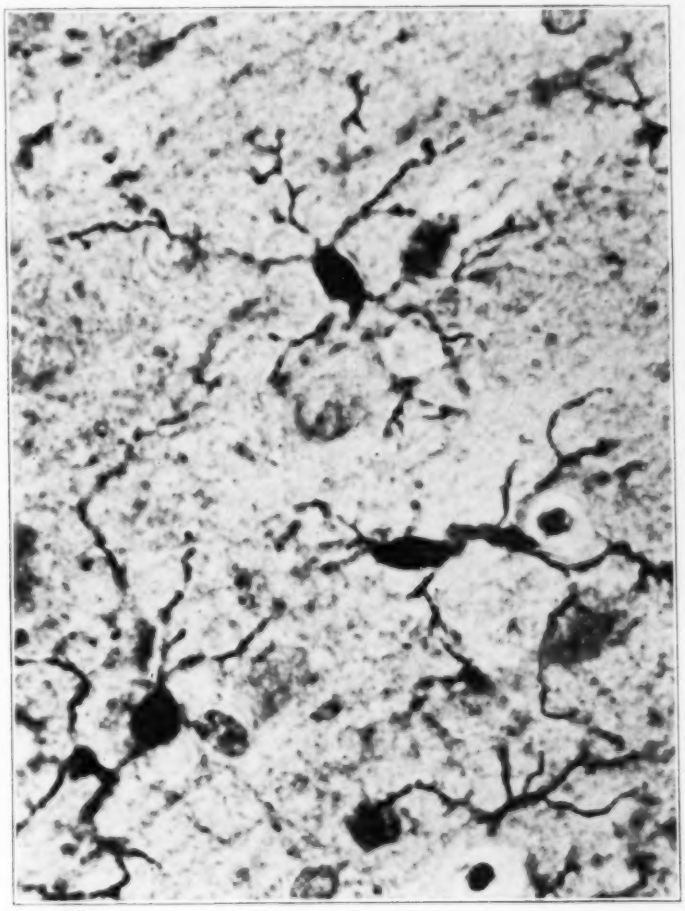

Fig. 2.—Normal microglia of the motor cortex. Silver carbonate Hortega; × 930. (Silver carbonate Hortega was used in staining all of the specimens appearing in figures 3 through 13, and 25 through 29.)

extra-adventitial vascular process. They were at all times outnumbered by cells of the mononuclear type. No plasma cells were identified with the routine stains.

No attempt will be made to comment on the problem of the relation of the so-called "endothelial leukocytes" to the cells of the microglial

series. The term "mononuclear" has been used to designate all the cells of the tissue in filtrate other than polymorphonuclear leukocytes and lymphocytes. With the routine stains it was possible to differentiate the small, dark, elongated nuclei "Staebchenzellen," and the minute, round nuclei of oligodendroglia cells, which were often seen as satellites to the neurons of the group surviving from 242 to 309 days. In preparations other than gold and silver impregnations, it was not thought possible to distinguish with any degree of certainty the macroglia nuclei from those of the microglia showing pathologic changes.

The glial reaction was carefully studied in cases 4, 5, 6 and 8, while silver impregnations on formaldehyde fixed material were also available in cases 3, 7 and 10, together with gold sublimate preparations in

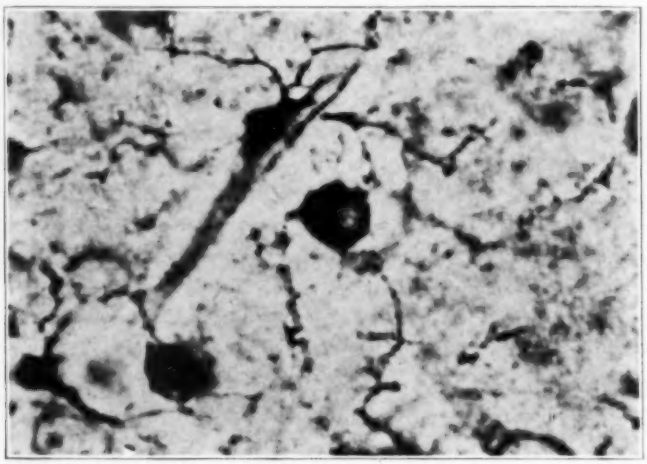

Fig. 3.—Normal oligodendroglia cells in the frontal cortex. Note the relative size of the microglia cells here and in figure 2; × 930.

cases 1, 3 and 10. There can be little doubt that the bulk of the focal infiltrate was composed of microglia cells. The changes from the normal microglia to compound granular corpuscles have been frequently and adequately described,[19] and are illustrated in figures from 4 to 11 inclusive. As a rule, mild damage to the nerve cells was accompanied by what might be termed pregitter cell changes in the microglia, whereas the destruction and disintegration of neurons called forth a response of granular corpuscles. These were rarely seen in cases in which only diffuse infiltration occurred. Since the lumbar

19. Kubie, L. S., and Shults, G. M.: Forced Drainage of Cerebrospinal Fluid in Relation to Treatment of Infections of the Central Nervous System, Arch. Neurol. & Psychiat. **19**:997 (June) 1928. Hurst (footnote 7).

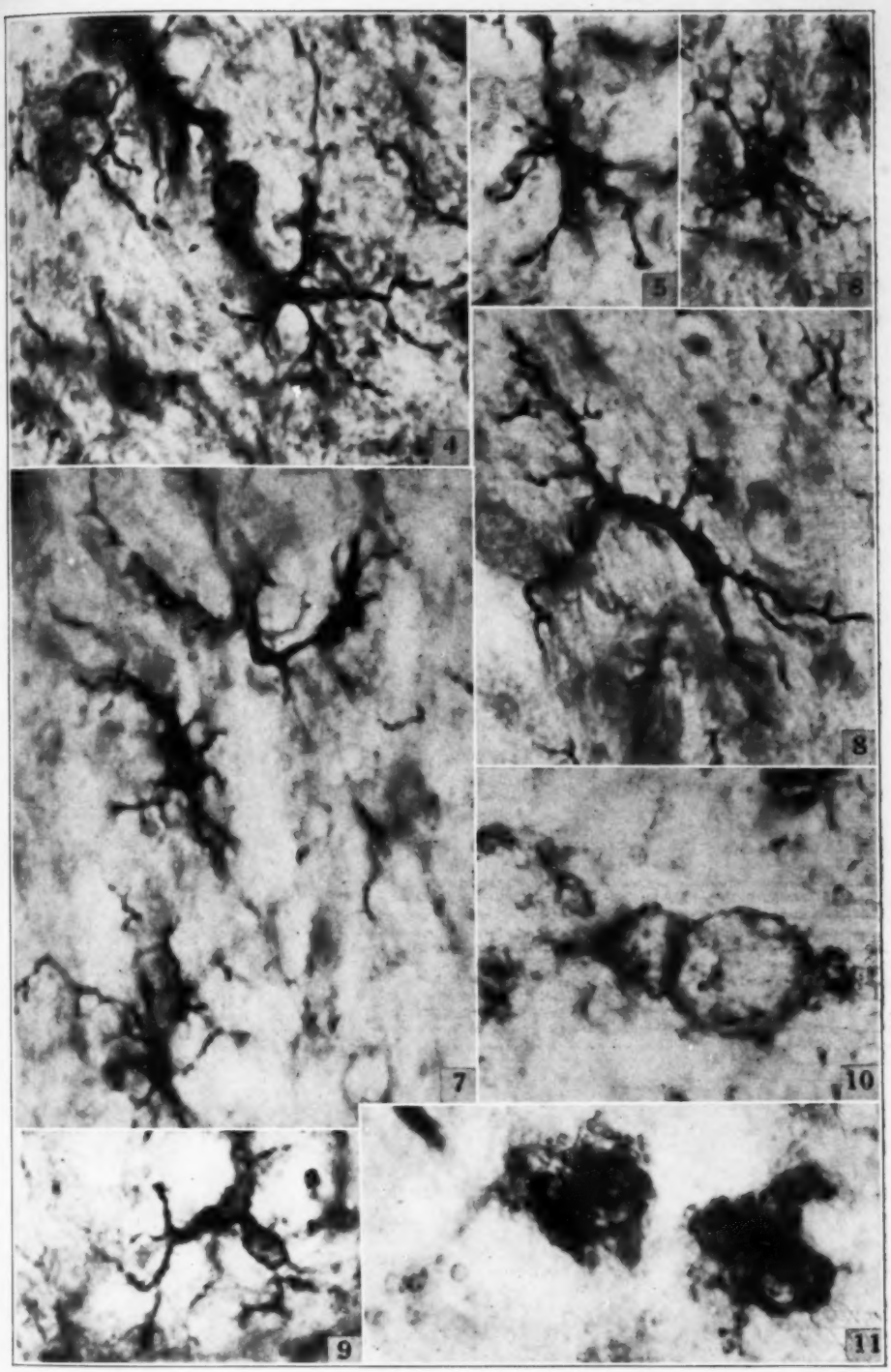

Fig. 4 (case 5).—Microglia cell in the medulla, showing shortening and thickening of the processes. The oligodendroglia cells show no pathologic changes; × 930.

Fig. 5 (case 5).—Microglia cell in the medulla, showing enlargement of the cell body and shortening and clubbing of the processes; × 930.

Figs. 6 and 7 (case 5).—Microglia cells in the medulla, with vacuolization of the cell body; × 930.

Fig. 8 (case 5).—"Staebchenzelle" in the medulla; × 930.

Fig. 9 (case 5).—Extensive vacuolization of a microglia cell (medulla); × 930.

Fig. 10 (case 6).—A typical gitter cell from the thoracic cord; × 930.

Fig. 11 (case 6).—Compound granular corpuscles laden with fat (lumbar cord). Several globules of lipoid are seen lying free in the tissues; × 930.

region was more severely affected than the higher segments of the cord, it follows that the more advanced stages of microglial activity were more common there than in the cervical region (figs. 12 and 13). Parallel to this situation was the finding of abundant extracellular and intracellular fat in the anterior horns of the lower levels, while diminishing quantities were present in the thoracic and cervical cords of the group surviving from 19 to 72 days. We confirm Hurst's observation

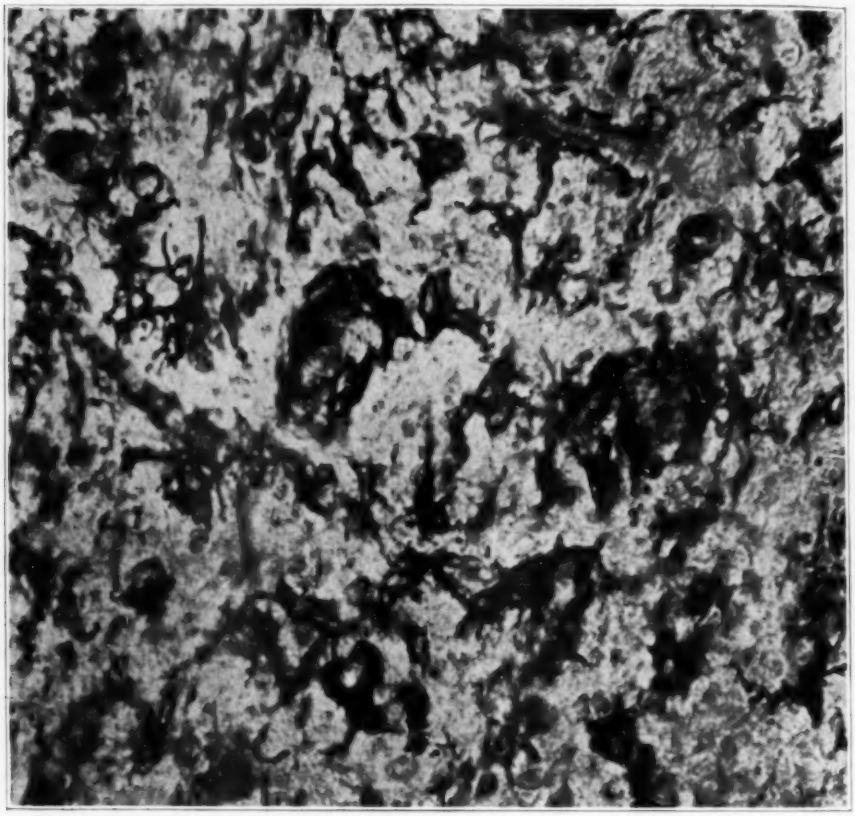

Fig. 12 (case 5).—Microglia showing pathologic changes in the area of destruction shown in figure 1; × 470.

that, while many gitter cells were filled with fat, others showed large vacuoles containing no Fettpenceau-staining globules. The pregitter forms were also seen to contain fat in areas in which masses of bright red lipoid material were lying free in the tissues. In areas of milder activity, microglia cells carrying fat were observed only about and in the perivascular spaces. Free fat was also present both in that location

and in the vascular lumina. No lipoid material was found in the gray matter of the cervical cords in cases 13 and 14.

The oligodendroglia cells, visible, although scanty, in the cross-sections of the cords of the normal controls, were conspicuous by their absence in the monkeys with poliomyelitis, although an occasional cell of this type was seen in the posterior horns. It is probable that these rather delicate structures succumbed to the virulence of the infectious process in the earlier cases. Unfortunately, silver impregnations in the group surviving from 242 to 309 days were not available, so that the prominence of satellitosis about the nerve cells of the older animals could not be definitely confirmed as oligodendroglial, although the nuclei were apparently characteristic of these cells.

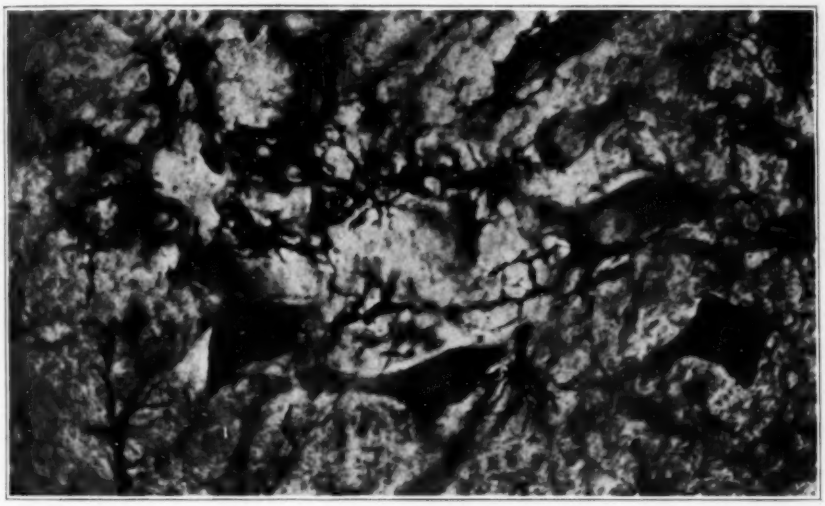

Fig. 13 (case 6).—Neuronophagia in the cervical cord. A group of phagocytic microglia cells are seen at the site of a degenerated nerve cell; × 470.

A comparison with normal tissues often revealed a generalized increase of both the fibrous and the protoplasmic astrocytes which was confined neither to the injured tracts nor to the areas of marked microglial reaction, although occasionally perivascular proliferation was seen. The cells themselves showed thick processes, frequently without secondary branches, heavy sucker feet and large, deeply impregnated cell bodies. Dividing cells were present, but rare. The areas of destruction showed a paucity of astrocytes consistent with the lack of fibrous replacement seen in the phosphotungstic acid preparations (fig. 1). In and near the periphery of these lesions the remaining cells were poorly stained and showed degrees of clasmatodendrosis varying from spirillar

degeneration to fragmentation of the processes and feeble impregnation of the cell bodies (fig. 14).

Destruction of the Nerve Cells.—Case 1 presented the typical picture of damage to the neurons described by Hurst. The anterior horn cells were for the most part necrotic masses, which called forth a response of polymorphonuclear cells and microglial phagocytes, or else, in the stages of acute degeneration in which the cytoplasm was ragged in outline, acidophilic and structureless, while the nuclei were absent or eccentric and deformed, ill-defined or hypochromatic. These far outnumbered the second cellular type which was shrunken, containing

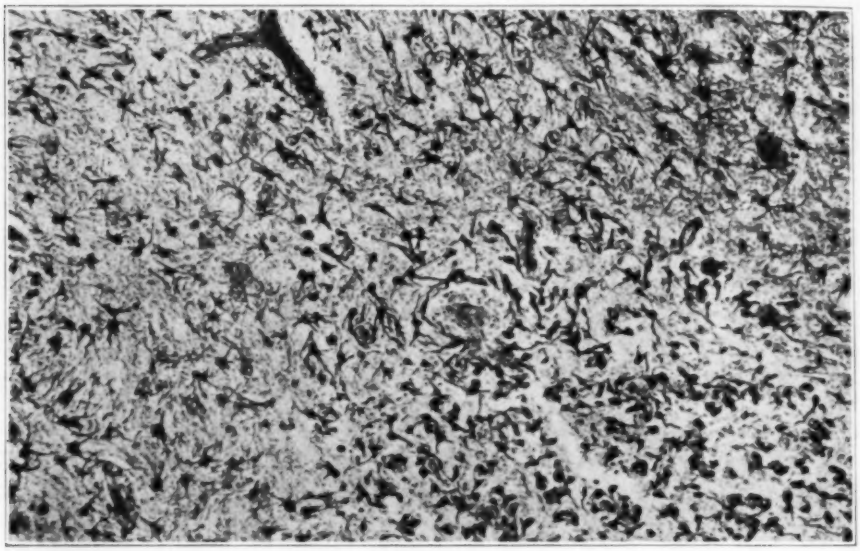

Fig. 14 (case 5).—Astrocyte proliferation in the area of destruction shown in figures 1 and 12. Clasmatodendrosis may be observed below and to the right of the vessel near the center of the field. The numerical increase of astrocytes in that location suggests that proliferation preceded degeneration. Cajal's gold sublimate; × 125.

hyperchromatic nuclei, and irregularly staining, often vacuolated cytoplasm in which no Nissl substance was distinguishable. These cells had been traumatized but were, in Hurst's terminology, "recoverable."

The degree of viability of these cells could be more definitely ascertained in the later stages in which acute degeneration was no longer present, but in which neuronophagia was prominent. In the group, surviving from 40 to 84 days, as well as in that comprising cases of longer duration, the numerical cell loss was variable, not only from monkey to monkey, but also from level to level within the same spinal

cord. In the lumbar region, the surviving nerve cells were fewer and more abnormal than in the cervical segments, the dorsal ranging between the two extremes (table 2). In the cases of intermediate duration, the shrunken cells were the predominating type and were characterized by hyperchromatism both of the cytoplasm and of the nucleus, by exaggeration of the processes, and by irregularity of contour or by their spindle shape (figs. 16 to 18). The Nissl substance was generally indistinguishable from the deeply staining cytoplasm, finely granular, or distributed about the cellular periphery. Nuclear detail was often similarly obliterated. Neurofibrils were occasionally visible at the proximal

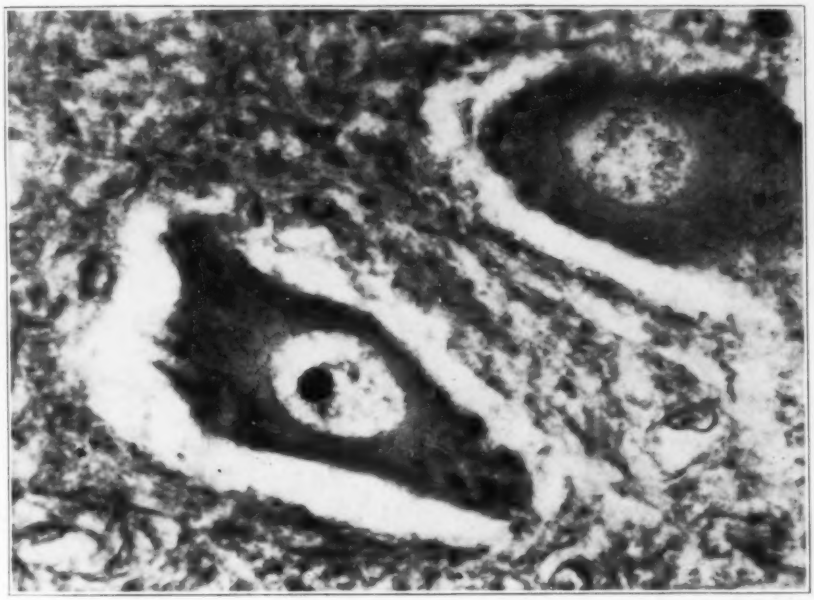

Fig. 15.—Normal anterior horn cells of the lumbar cord. Phosphotungstic acid and hematoxylin; × 1,050.

end of the processes, but, owing to the deep black impregnation to which these cells were subject in the Bielschowsky preparations, they could rarely be traced beyond that point. When distinguishable, the fibrillar substance was granular and not clearly demarcated.

While many of these neurons were evidently injured but still viable, others, which had partially succumbed, were paler, more vacuolated and less regular in outline. The nuclei were on the whole better preserved than the cytoplasm. Microglial phagocytosis was frequently present. There was also a variable number of cells approximating the normal, generally near the periphery of the anterior horns.

In the group surviving from 242 to 309 days the numerical cellular decrease was greater in some instances, but the surviving cells showed few deviations from the normal other than slight distortions of contour and of the fibrillar network, which was sometimes knotted and clumped. In the proximal portions of the anterior horns, shrunken cells of the type previously described were often seen (fig. 19). In contradistinction to the earlier cases, satellitosis rather than neuronophagia was a common observation (fig. 21).[20]

The same kind of destruction of the neurons, although in respectively diminishing degrees, was also present in the columns of Clarke, in the lateral horns and in the cells of the posterior horns. Although these

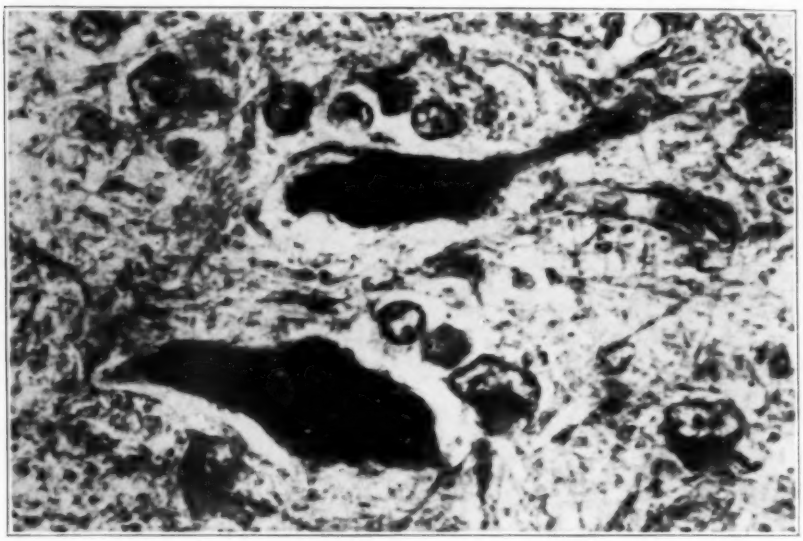

Fig. 16 (case 5).—Section showing shrunken cells. Compare with similarly located anterior horn cells in figure 15. Phosphotungstic acid and hematoxylin; × 1,050.

lesions may at times appear to be insignificant in comparison with the more dramatic process in the anterior horns, the disturbances of the sensory fiber tracts shown by the Weigert preparations, clearly demonstrate the degree of damage.

Figure 22 illustrates the characteristic picture of the cervical cords in which the outstanding lesion was that of the dorsal spinocerebellar

20. The term neuronophagia has been used in the narrower sense implying phagocytosis of damaged cells by microglial phagocytes, whereas satellitosis has been taken to signify the multiplication of oligodendroglia and microglia about apparently intact cells.

tract the fibers of which arise from the cells of Clarke's column. The tract of Goll remained intact, whereas degeneration of the fibers in the cornucommissural zone was seen in the areas which, in all probability, correspond to the neurons of association of cells which lie in the posterior horns. Similarly, in the lateral columns, injury to secondary neurons, the cells of which are located in the lateral portion of the anterior horns and at the base of the posterior horns, may be made responsible for damage to the lateral spinocerebellar and lateral spinothalamic tracts respectively. Only the dorsal spinocerebellar tracts were fairly constantly involved, whereas a patchy distribution of the injury to the other pathways, including the lesions in the anterior columns, gave

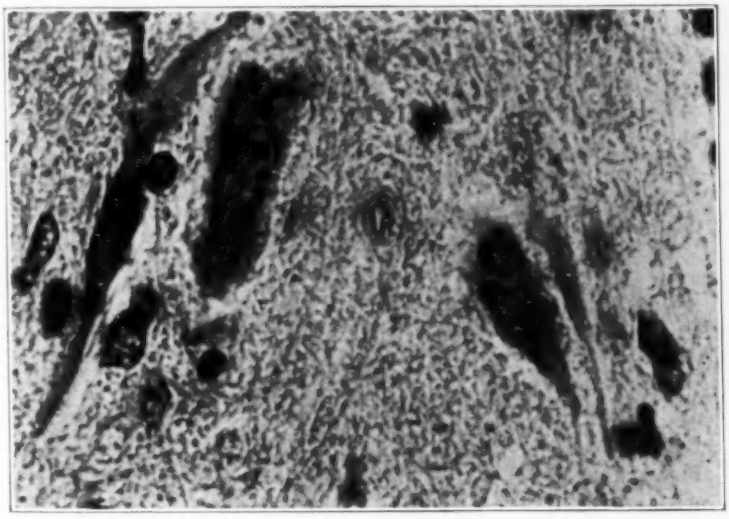

Fig. 17 (case 5).—Spindle cells in the anterior horn of the lumbar cord. Phloxine-methylene-blue; × 1,050.

evidence to the irregularity of the disease process. It is possible that the lesions in the roof and the red nuclei may be made responsible for the injury to their spinal pathways.

The Fettpenceau stains showed little fat in the fiber tracts of the group surviving from 40 to 52 days, and although occasionally small focal areas in the lateral columns or diffuse droplets in the cornucommissural zone were seen, the dorsal cerebellar tracts remained strikingly free from them. On the other hand, diffuse fatty degeneration was observed in the anterior and lateral columns and in the indirect posterior column pathways in cases 9 and 10, while cases 13 and 14 showed masses of fat in the dorsal cerebellar tracts.

The anterior roots of the lumbar cords were often infiltrated with fat, and the medullated fibers leading to them frequently showed degeneration. This occurred more rarely at the higher levels of the cord. No study of the peripheral nerves was undertaken.

Table 2 summarizes the perivascular, tissue, and nerve cell reactions according to an empirical scale ranging from mild to severe, according to the number of cells involved in the lesions, in order to compare the relative severity between levels and between cases. An

TABLE 2.—*Spinal Cord*

		Lumber			Thoracic			Cervical		
Case	Days	Perivascular Infiltration	Tissue Infiltration	Degeneration of the Nerve Cells	Perivascular Infiltration	Tissue Infiltration	Degeneration of the Nerve Cells	Perivascular Infiltration	Tissue Infiltration	Degeneration of the Nerve Cells
1	19	Moderate	Severe	Severe	Mild	Moderate	Moderate	Mild	Severe	Severe
2	29	Mild	Mild	Mild	Mild	Mild	Moderate	Moderate	Moderate	Moderate
3	40	Moderate	Severe	Severe	Severe	Moderate	Moderate	Moderate	Severe	Moderate
4	41	Severe	Severe	Severe	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
5	47	Severe	Severe	Severe	Mild	Moderate	Moderate	None	Severe	Moderate
6	47	Moderate	Severe	Severe	None	Mild	Moderate	Mild	Severe	Moderate
7	48	Severe	Severe	Severe	Mild	Moderate	Moderate	None	Moderate	Moderate
8	52	Severe	Severe	Severe	Moderate	Severe	Severe	Mild	Moderate	Mild
9	50	Severe	Severe	Severe	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
10	72	Mild	Severe	Severe	Moderate	Severe	Severe	Mild	Moderate	Mild
11	84	Severe	Moderate	Moderate	Moderate	Mild	Moderate	Mild	Moderate	Mild
12	242	Mild	Moderate	Moderate	Mild	Mild	Mild	Mild	Moderate	Moderate
13	259	Moderate	Moderate	Moderate	None	Mild	Moderate	Moderate	Severe	Moderate
14	267	None	Mild	None	Mild	Mild	Mild	None	Mild	Mild
15	309	Mild	Moderate	Severe	None	Mild	Moderate	None	Mild	Moderate

estimate of this kind is necessarily inexact and is presented merely in the form of a key map to the preceding description.

SPINAL GANGLIA

Diffuse and focal lymphocytic infiltrates were present in the spinal ganglia in cases 4 to 6, and in cases 11 to 15 and were absent only in case 9. These, at times, replaced disintegrating ganglion cells. An increased number of capsular cells was probably more apparent than real, since the appearance of proliferation was often given by tangential sections (fig. 23). Microglial activity was not shown in case 4 on

which silver impregnations were made and in which the lymphocytes were numerous.

MEDULLA AND PONS

Here, as in the cord, pial infiltration was minimal and confined to a few cells about the anterior fissure and the nerve roots. At the level of the pyramidal decussation, the picture presented by the anteriorly situated motor nuclei was essentially that of the anterior horns at the lower levels, for extensive perivascular and tissue infiltrates, together with destruction of the nerve cells, were frequently present. The nuclei gracilis and cuneatus, on the other hand, were generally intact, and

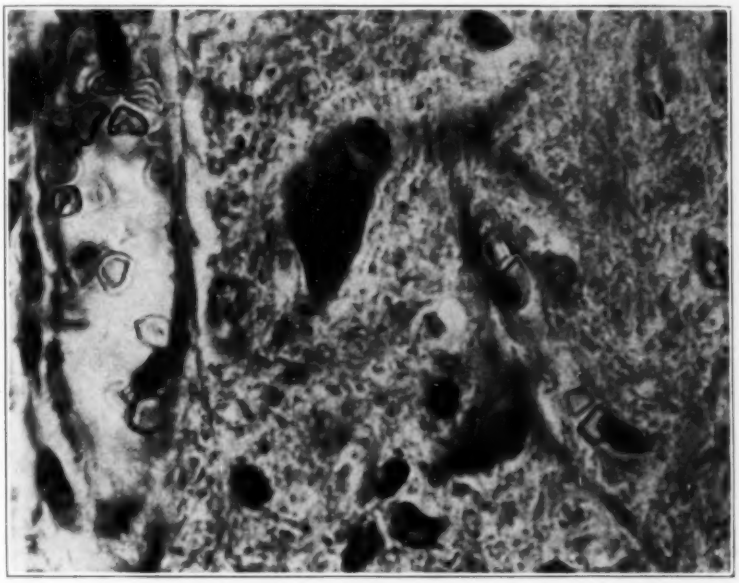

Fig. 18 (case 5).—Deformed nerve cells in the lumbar cord, showing sharply demarcated basophilic processes. No cellular structures other than the clumped Nissl substance of the upper cell are distinguishable. The nucleus of a mononuclear cell may be seen lying on each nerve cell. These should not be regarded as neuronophages in that they lie above the plane of the two neurons. Phloxine-methylene-blue; × 1,050.

even when inflammatory lesions occurred in the posterior half of the medulla, only the mildest grade of disturbance of the neurons was observed.

At the higher bulbar levels this apparent preservation of the nerve cells was even more remarkable in that, in the presence of frequent infiltrative inroads, the neurons showed only minor grades of degeneration, although glial response to these cells was the rule. In the group surviving from 19 to 52 days, the perivascular lesions were at times

so intense as to obliterate the nucleus of a cranial nerve totally or in part, so that, as in the cords, there were areas in which the parenchyma was totally or partially replaced by the perivascular and tissue infiltrates, together with capillary proliferation, but even there the cells lying near the periphery of this zone were no more severely damaged than

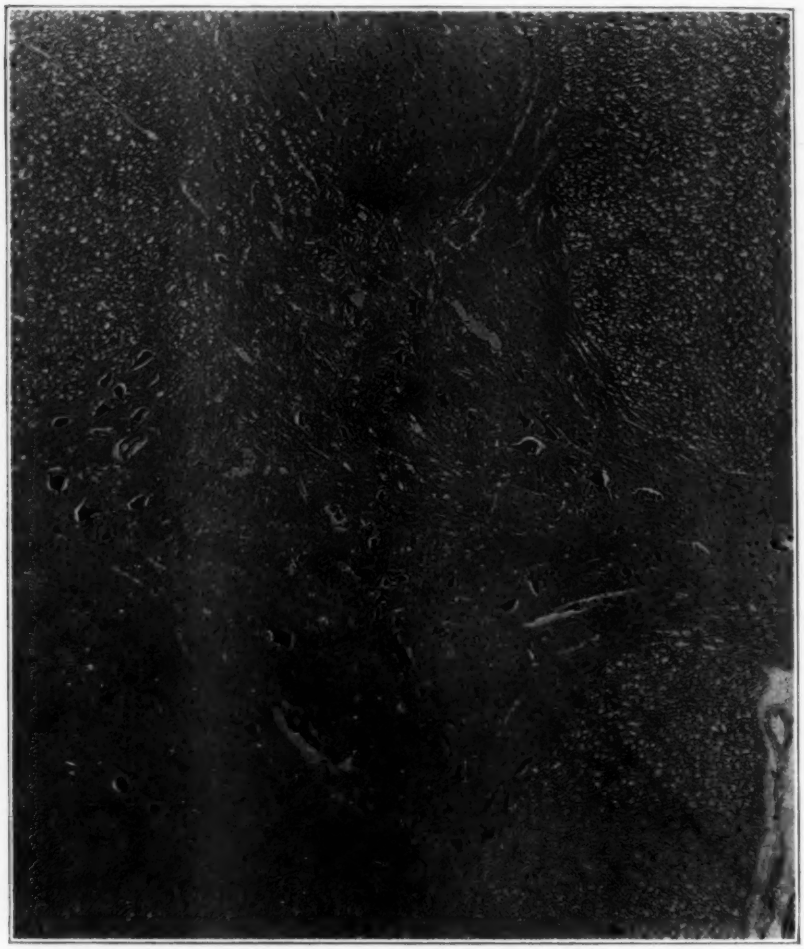

Fig. 19 (case 14).—The cervical cord of an animal that survived for 267 days after the onset of symptoms. There is no evidence of scar formation. Phloxine-methylene-blue; × 165.

those at a little distance. Neurofibrillar stains were of little assistance in proving this apparent cellular integrity, as the impregnations were for the most part not entirely satisfactory or dependable. No degeneration of the tracts or the fibers was seen in the Weigert preparations.

Since the perivascular lesions occurred most frequently near the midline, about the vessels of the anterior fissure, under the floor of the fourth ventricle, and near the angle of its floor with its lateral wall, the nuclei of the cranial nerves that suffered most severely were the hypoglossal, the vestibular, Deiter's nucleus and the dorsal tenth. Lesions

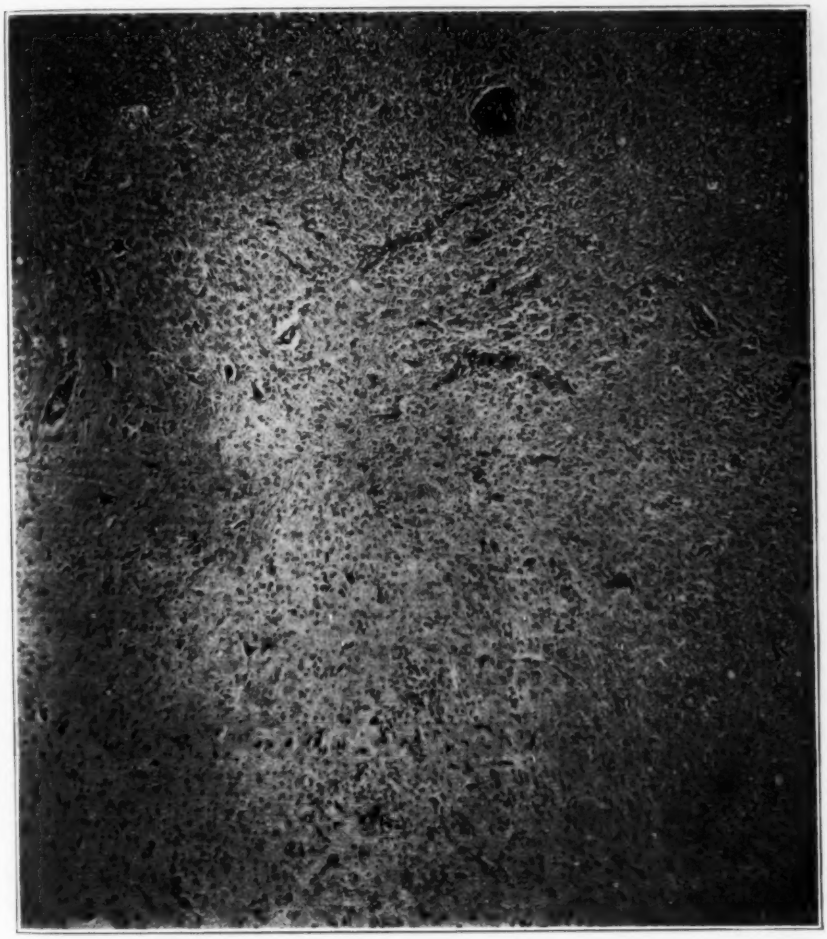

Fig. 20 (case 3).—The lumbar cord of an animal that survived for forty days after the onset of symptoms, showing extensive diffuse and focal tissue infiltration and a moderate perivascular reaction. Compare with figure 19 and table 1. Hematoxylin and eosin; × 165.

involving the twelfth nucleus often extended to the solitarius, and scattered patchy inroads on all the other nuclei of the cranial nerves were found at various levels in different monkeys, regardless of

their motor or sensory character, and dependent only on their casual location in the path of a perivascular lesion. The olives were often spared, although perivascular infiltrates were not uncommon in the substantia reticularis dorsal to them. Sections cut through a higher level of the medulla tended to show fewer lesions, so that the sixth nucleus was less often involved than the twelfth.

The reaction of the tissues was both diffuse and focal, the microglial activity varying with the intensity of the inflammatory process. Case 5 showed a generalized proliferation of astrocytes.

In the group surviving from 242 to 309 days, only longitudinal sections of the medulla were available, which could not be compared directly with the cross-sections in the other cases. Nevertheless, it was

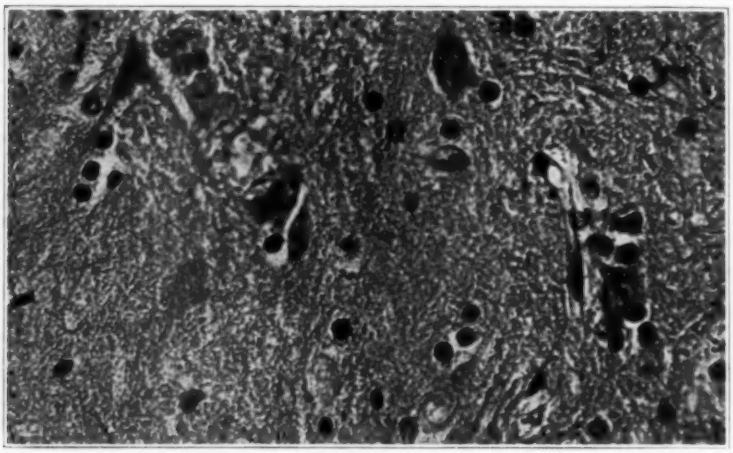

Fig. 21 (case 12).—Satellitosis in the lumbar cord of a monkey that survived for 242 days. Neuronophagia may also be seen about the two pale nerve cells lying near a deformed cell with four satellites. Phloxine-methylene-blue; × 440.

possible to ascertain that no perivascular lesions were present. In case 5 the glia nuclei about the apparently intact nerve cells showed a numerical increase over the normal.

MIDBRAIN

As the medulla, taken as a whole, showed less serious damage than the spinal cords, so the midbrain in cases 1, 3, 4, 5, 6, 7, 10 and 11 gave less evidence of inflammatory lesions than the lower brain stem. Hurst described the perivascular infiltration about the aqueduct in acute poliomyelitis as "more intense than at any other level." Large lesions of this character were seen about the iter in cases 1 and 3, but of the other seven monkeys only one (case 6) showed a mild perivascular

reaction in that location. The red nucleus and the substantia nigra were extensively involved, while smaller perivascular lesions were found in the substantia reticularis near the midline and occasionally in the quadrigeminal plate.

Of the oculomotor and trochlear nuclei, and of the cells in the corpora quadrigemina, it is only possible to state that the cells showed mild changes in the face of infiltrates immediately adjacent to them, but that silver impregnations revealed marked proliferation of the microglia cells about them. Gitter forms were rare except in the red nucleus. Here the astrocytes showed clasmatodendrosis in the cases in which perivascular lesions caused advanced cellular destruction. It was characteristic of the patchy poliomyelitic invasion that occasionally one red nucleus was entirely obliterated while the other showed only the mildest changes. The cellular reaction corresponded to that in the anterior horns of the spinal cord. There were pale cells that had lost

TABLE 3.—*Incidence of Perivascular Lesions*

Midbrain	Cases Examined	Cases Showing Perivascular Lesions
Corpora quadrigemina	8	5
Dorsal midbrain below aqueduct	7	6
Red nucleus	7	6
Substantia nigra	6	5

their stellate form and in which the cytoplasm was poorly defined while the nucleus was still distinctly visible. These were subject to neuronophagia of a type that heralded their ultimate removal. The second type of degeneration was represented by all the phases of shrinkage and hyperchromatism. Many cells were totally destroyed.

The status of the substantia nigra was similar to that of the red nuclei, although the cellular damage was usually not so great.

BASAL GANGLIA

The incidence of lesions in the basal ganglia, as shown in table 4, serves to demonstrate the relative immunity of the striate body as compared to the globus pallidus and the thalamus. Perivascular lesions were less frequently present near the ventricular wall than in the neighborhood of the internal capsule, and it was in this region also that the pallidum was most frequently involved, although invariably to a lesser degree than the thalamus. The lesions in the putamen in case 4 were composed of only a few cells in the perivascular spaces.

Destruction of the nerve cells was never demonstrated with the routine stains, and only mild changes were noted, although tissue

infiltration and neuronophagia accompanied the perivascular lesions. Silver impregnations in cases 4, 5, 6 and 8 showed advanced microglial activity in the thalamus and milder reactions of the same type in the globus pallidus. At times fat could be demonstrated about the perivascular spaces and in the vascular lumen, but cells containing fat were not seen in the tissues. The astrocytes in cases 5 and 6 gave evidence of clasmatodendrosis in the thalamus and showed no proliferation elsewhere.

TABLE 4.—*Incidence of Infiltrative Lesions in the Basal Ganglia*

Case		Caudatus	Putamen	Pallidum	Thalamus
1	Perivascular infiltration	+	+	+	+
	Tissue infiltration	+	+	+	+
2	Perivascular infiltration	0	0	+	+
	Tissue infiltration	0	0	+	+
3	Perivascular infiltration	0	0	0	+
	Tissue infiltration	0	0	0	+
4	Perivascular infiltration	0	+	+	+
	Tissue infiltration	0	+	+	+
5	Perivascular infiltration	0	0	0	+
	Tissue infiltration	0	0	0	+
6	Perivascular infiltration	0	0	..	+
	Tissue infiltration	0	+	+	+
7	Perivascular infiltration	0	0	0	0
	Tissue infiltration	0	0	0	0
8	Perivascular infiltration	0	0	..	..
	Tissue infiltration	0	0	..	..
9	Perivascular infiltration	0	0	0	0
	Tissue infiltration	0	0	0	0
10	Perivascular infiltration	0	0	+	+
	Tissue infiltration	0	0	+	+
11	Perivascular infiltration	0	0	0	+
	Tissue infiltration	0	0	0	+
12	Perivascular infiltration	0	3	0	0
	Tissue infiltration	0	0	0	0
13	Perivascular infiltration	0	0	..	..
	Tissue infiltration	0	0	..	..
14	Perivascular infiltration	0	0	..	+
	Tissue infiltration	0	0	..	+
15	Perivascular infiltration	0	0	0	+
	Tissue infiltration	0	0	0	+

HYPOTHALAMUS, AMYGDALOID NUCLEUS AND GENICULATE BODIES

Large perivascular and infiltrative lesions were frequently seen in the lamina terminalis, in the hypothalamic region and in and near the amygdaloid nuclei. The geniculate bodies were studied in only a few cases, and in these no pathologic changes were found.

CORTEX

The cortices of nine monkeys were examined. In cases 1, 3, 7 and 10 they were stained with hematoxylin and eosin. Celloidin sections had been cut through the whole brain so that not only both hemispheres but

several sections through each lobe of the cerebrum could be studied. This afforded a good general picture, but was unsatisfactory from the point of view of detailed cellular structure. It was difficult to compare these with the thin paraffin preparations of the cortices in cases 4, 5, 6, 8 and 14 which were stained with phloxine-methylene-blue (methylthionine chloride, U. S. P.). Silver impregnations for microglia, oligodendroglia and neurofibrils were made of the cortices in cases 4 and 8, while all stains and impregnation were possible on two monkeys (5 and 6). In the second group of five cases, not more than one section through each cortical area was available. It follows that since the inroads of poliomyelitis are notoriously patchy in distribution,

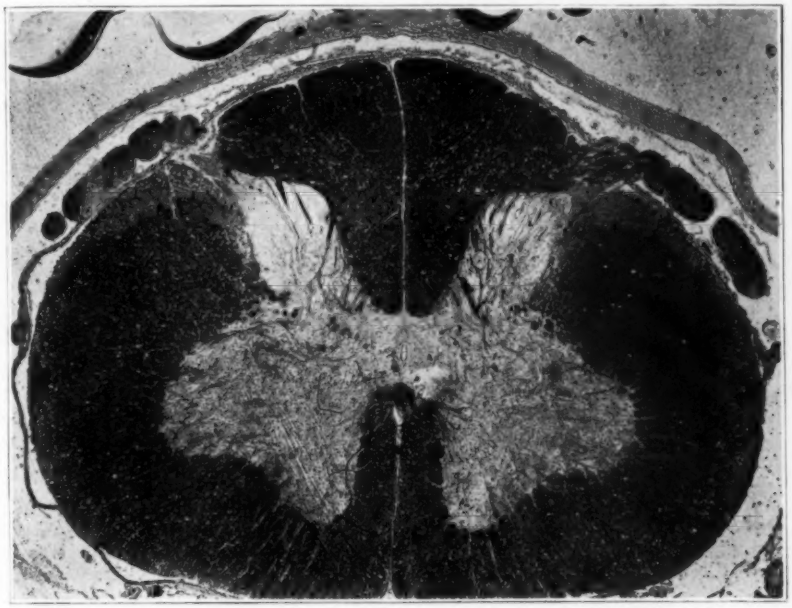

Fig. 22 (case 6).—Section of the cervical cord. The dorsal columns are spared except for the cornucommissural zone. The outstanding lesion is that of the dorsal spinocerebellar tracts, while diffuse degeneration may be seen in the lateral and anterior columns. Weigert-Kulschitsky; × 16.

the following description of the pathologic changes may be considered somewhat fragmentary.

Pial Infiltration.—The meningeal reaction was slightly more marked over the cortices than over the spinal cords. Here again case 1 approximated the acute picture, for polymorphonuclear cells were seen, whereas in the other cases the pial infiltrate was composed of lymphocytes and mononuclear cells. These were few in number and were usually found

contiguous to vessels or in the depths of fissures. In the group surviving from 40 to 72 days, a slight leptomeningitic reaction was present over the motor and insular cortex of four monkeys, over the occipital and temporal areas of three, and over two of the three frontal sections which were examined.

Perivascular Infiltration.—Although perivascular lesions were far less prominent in the cortex than at the lower levels, case 1 showed

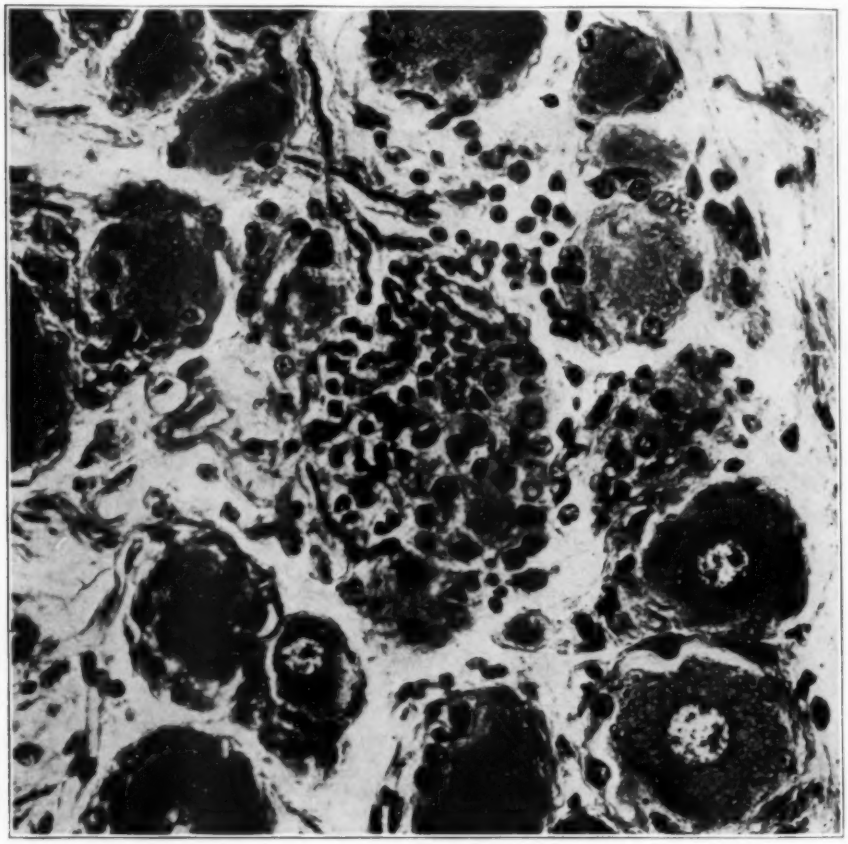

Fig. 23 (case 14).—Section of the spinal ganglion. A focus of lymphocytic infiltration overlying several disintegrating ganglion cells the capsule cells of which are still clearly visible. To the right a clump of capsular cells may be seen. Phosphotungstic acid and hematoxylin; × 440.

extensive infiltration about the large vessels from the periphery and about the smaller ones in the deeper cortical layers. Here, too, cells penetrated the perivascular spaces into the adjacent tissues. Of the eight other monkeys, only case 3 showed radial lesions in the motor

area, while perivascular infiltrates of an extensive character were also seen in this monkey and in case 5. In general, the number of mononuclear cells and lymphocytes in the Robin-Virchow spaces formed only a thin cuff about the lumen of the smaller vessels.

Focal areas of destruction of the type seen in the spinal cords were rarely noted except in case 1. At times capillary proliferation was present in areas of deterioration of the nerve cells and glial infiltration, in which no perivascular lesions occurred.

Tissue Infiltration.—A degree of focal and diffuse tissue infiltration which was not approximated in any other instance was found in case 1, in which many more lymphocytes were present than in the tissues from cases of longer standing. In general, the microglial proliferation bore a direct relationship to the damage to the nerve cells and to the perivascular reaction. There were few independent focal lesions. Gold sublimate

TABLE 5.—*Incidence of Perivascular Lesions*

Cortical Area	Cases Examined	Cases Showing Perivascular Lesions
Anterior frontal	6	2
Motor area	8	6
Insula	7	3
Temporal	8	1
Occipital	7	1
Ammon's horn	8	1

impregnations were available only in cases of the group surviving from 40 to 52 days. In case 6 there was definite proliferation of astrocytes in the motor cortex (fig. 24) not unlike that described in dementia paralytica.[21] Comparison with the macroglia of the normal cortex in this area shows the glia cells to be more deeply impregnated and to possess coarser, shorter, frequently unbranched processes, and thick, long sucker feet. Dividing cells, but no astroblasts, were seen. Unfortunately, there were no preparations made from material taken from the group surviving from 242 to 309 days, so that this reaction of the astrocytes could be traced no further.

Due to the thickness of the hematoxylin and eosin sections, an accurate estimate of the tissue infiltration in cases 1, 3, 7 and 10 could not be made, although it was possible to form a relative judgment on the cases as a whole, when comparison was made with similar material from normal monkeys. In cases 4, 5, 6 and 8, the cells shown by the phloxine-methylene-blue stain could be roughly correlated with the silver impregnations in which the nerve cells were frequently visible also.

21. Ramón Cajal, S.: Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:738, 1926.

It was found that while the damage to the neurons was frequently mild, judging by the routine stains, microglial proliferation about them was frequent and widespread, but silver impregnations of cortical areas which were extensively affected showed no compound granular corpuscles. Figures 25 and 26 illustrate the various pathologic microglia

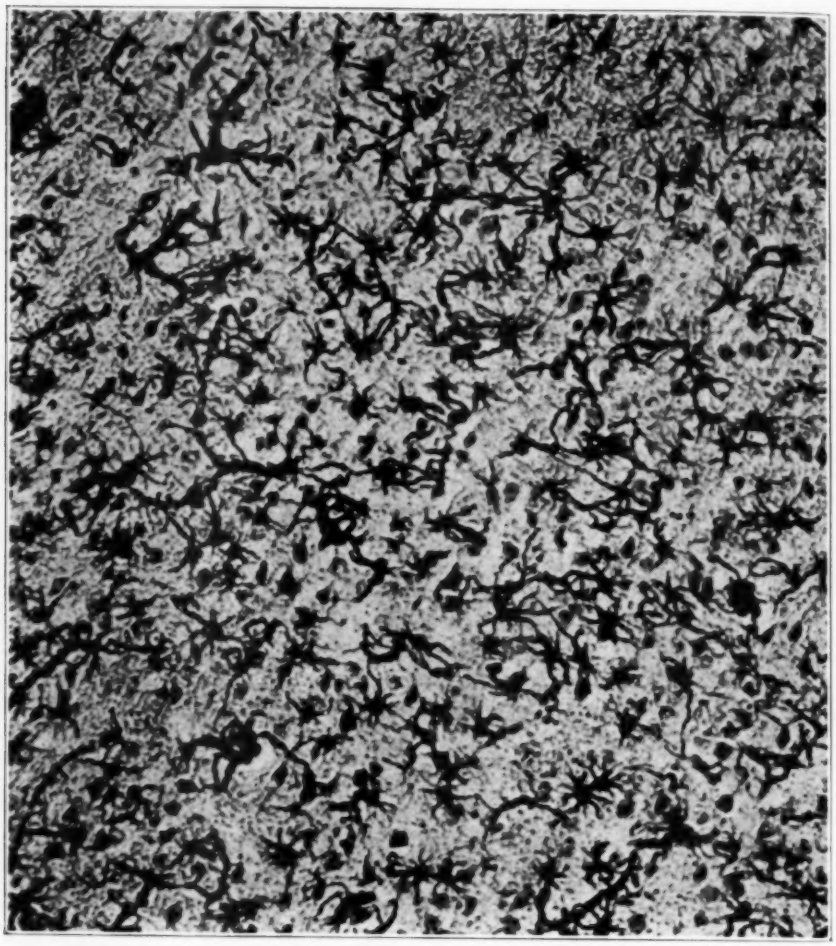

Fig. 24 (case 6).—An area of the precentral cortex showing hypertrophy and proliferation of the astrocytes; dividing cells may also be seen. Note the thick vascular attachments. Cajal's gold sublimate; × 220.

cells and their relation to degenerating neurons and proliferating capillaries. The section was cut from the same block as that in figure 24 and shows approximately the same cortical area as that in which astrocyte proliferation was demonstrated.

Swollen oligodendroglia were practically never seen. These cells were constantly and uniformly well defined in the sections stained by silver impregnation. In common with the microglia they were more heavily stained in the monkeys with poliomyelitis than in the normal controls, and while their number appeared to be somewhat increased

Fig. 25 (case 6).—Section showing the microglial reaction in precentral area of the cortex shown in figure 24. Above and to the right of the perivascular lesion is a focus of advanced destruction of the nerve cells and microglial proliferation. Below microglia cells may be seen lying about nerve cells and capillaries. The oligodendroglia shows no pathologic changes; × 220.

in the cortex, this observation may have been more apparent than real, owing to their increased visibility (figs. 27 and 28). Such changes in the cytoplasm as were present were observed in the normal controls also.

Destruction of the Nerve Cells.—Degeneration of the nerve cells was more prominent in the anterior frontal, precentral and postcentral areas than elsewhere in the cortex, although no lobe remained consistently free from lesions. The approximate incidence of damage to the neurons, regardless of degree, is shown in table 6, which excludes case 1 on the ground that lesions were found in all areas throughout the cortex, whereas the lobular distribution in the other cases was by no means uniform, and demonstrated the scattered character of the poliomyelitic inroads.

The fact that degeneration of the nerve cells bears no direct relationship to perivascular infiltration has frequently been discussed in connection with acute poliomyelitis, and was again demonstrated in the cortices of monkeys with the chronic disease. The architecture remained intact except for the rare perivascular and infiltrative encroachment on it. In the cortex as in the basal ganglia, it was striking that the cells at the periphery of the lesions frequently showed no more advanced

TABLE 6.—*Incidence of Degeneration of the Nerve Cells*

Cortical Area	Cases Examined	Cases Showing Degeneration of the Nerve Cells
Anterior frontal	5	5
Precentral and postcentral	8	7
Insula	7	2
Temporal	8	4
Occipital	6	4
Ammon's horn	7	4

changes than those at a distance. There appeared to be little specificity regarding the cellular layers attacked, and scattered areas of degeneration of the small neurons were seen here and there throughout the cerebrum. On the other hand, the Betz cells and the deeper strata of the motor cortex were affected consistently, and where lesions were present in Ammon's horn, they were often confined to the hippocampal gyrus.

The large motor neurons showed degeneration not unlike the milder forms of disturbance described in the anterior horns of the spinal cord. Pale cells showing loss of angularity, faintly staining cytoplasm and an eccentric but visible nucleus were in the minority. By far the more usual type were nerve cells that showed a tendency to shrinkage and staining abnormalities. Figure 31 represents a Betz cell in which the Nissl substance forms a thin marginal ring, and in which the cytoplasm stains a structureless reddish-purple merging into a bright basophilic patch at one pole. The nucleus is eccentric and the nucleolus is present, but the chromatin bodies are not clearly visible. The processes are faint and basophilic. In the hematoxylin and eosin preparations, cells of this general conformation frequently show a red nucleolus, and, where degeneration has proceeded a little further, a structureless red

nucleus. In figure 32 a large motor neuron appears angular, shrunken, ragged and hyperchromatic. The Nissl substance is clumped, and the nuclear structure is no longer discernible. Another cell of the same type (fig. 33) has degenerated even further; it is deeply hyperchromatic and small, and approaches the spindle shape.

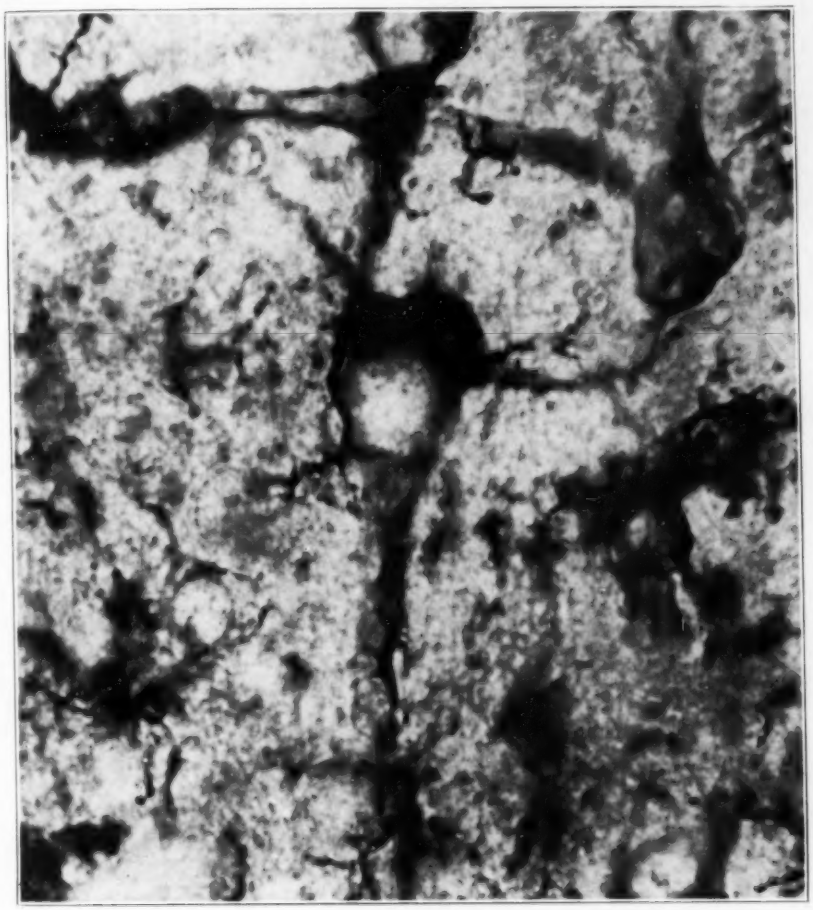

Fig. 26 (case 6).—Detail from figure 25. Note the microglia cells surrounding the cell body and axon, and lying on the capillary above the neuron; × 930.

Similar changes occurred in the smaller cortical cells, although the more minute details were indistinguishable in the specimens stained with the routine stains and in those from monkeys 5 and 6, stained with cresylecht violet. When stained with hematoxylin and eosin, the majority of cells which appeared to be pathologic were spindle-shaped

and showed basophilic nuclear degeneration and deeply acidophilic cytoplasm. In the phloxine-methylene-blue or phosphotungstic acid stains, the nuclei either remained clearly visible or became uniformly and deeply purple (fig. 34). The smaller pyramidal cells often did not elicit a tissue reaction, but in other instances cells that were apparently not abnormal in other respects were surrounded by nuclei of small cells, the character of which could not be precisely determined with the routine stains, but which appeared to be microglia and oligodendroglia.

As some of the staining reactions which were regarded as abnormal in the less severe cellular changes might have been due to technical

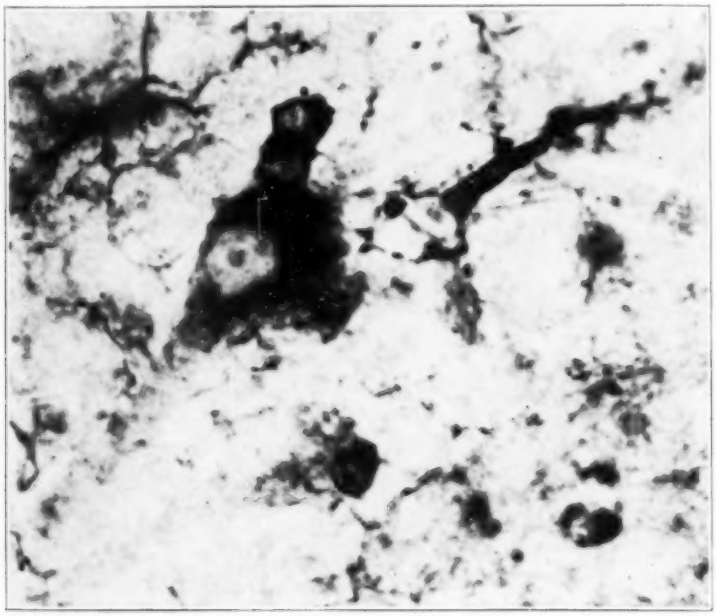

Fig. 27 (case 5).—A cell from the precentral cortex with two oligodendroglial satellites and one microglial neuronophage. The other two microglia cells may not be connected with the neuron; × 930.

errors, an attempt was made to impregnate the neurofibrils in cases 4, 5, 6 and 8. The results were variable both in the monkeys with poliomyelitis and in the normal controls, so that only such sections were considered reliable as showed an intact fibrillar system in the presumably normal cells while demonstrating various phases of neurofibrillar degeneration in others. The axonal fibers showed disturbances more rarely than the intracellular network, which frequently appeared to be fragmented or destroyed. The evidence derived from this method failed to solve the problem of the number of cells affected in a given area, owing to the irregularity of the impregnation.

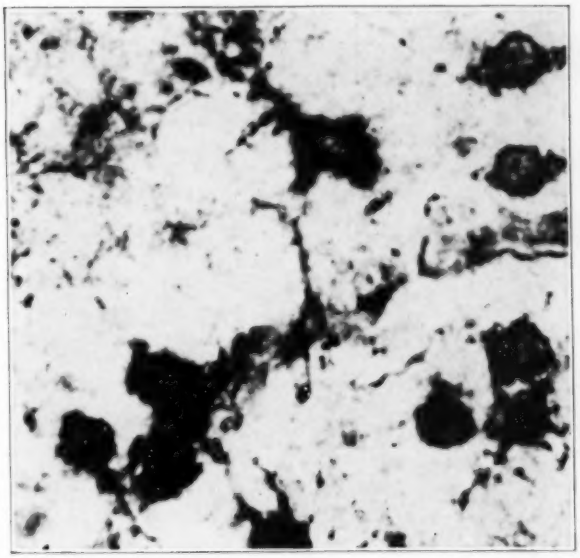

Fig. 28 (case 6).—Oligodendroglia cells on and about a capillary of the precentral cortex. A microglia cell showing pathologic changes is seen above the vessel; × 930.

Fig. 29 (case 6).—Microglia cells showing pathologic changes in an area adjacent to that shown in figure 28; × 930.

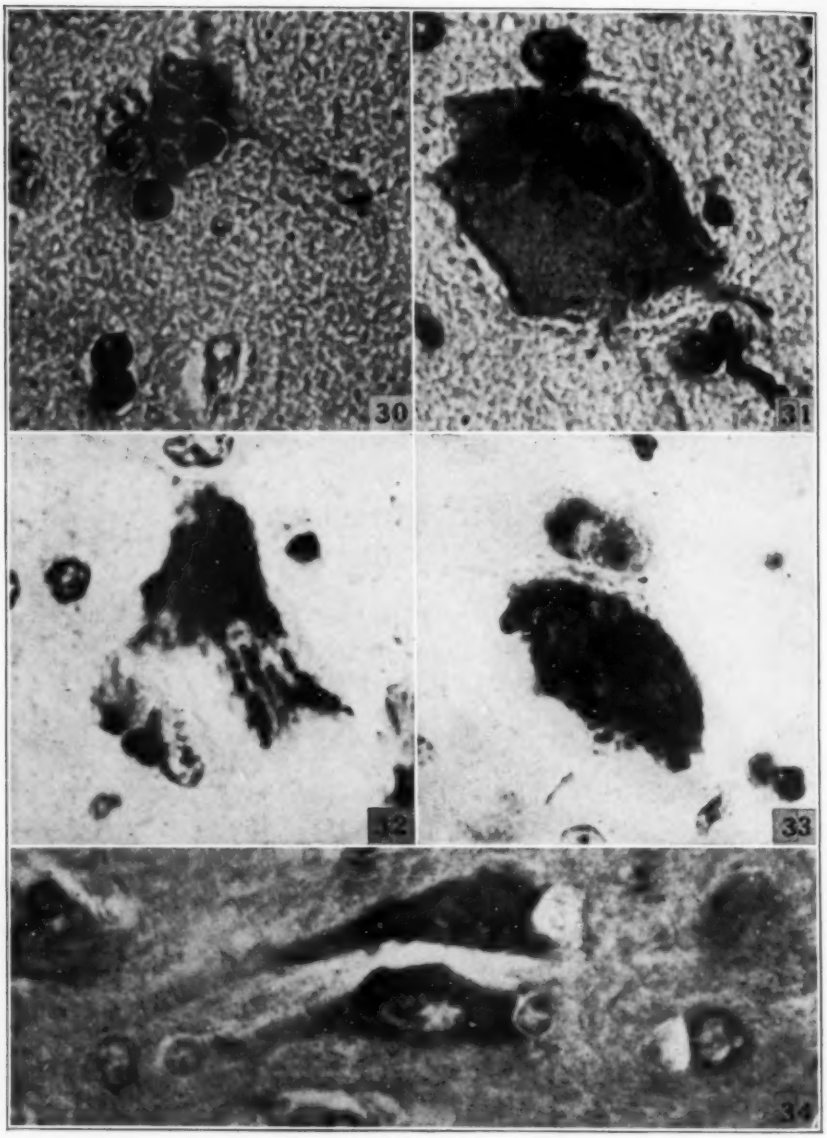

Fig. 30 (case 5).—Section of the precentral cortex showing a focus of mononuclear nuclei at the site of a cell that is distinguishable only by the projection of two faintly staining processes. Phloxine-methylene-blue; × 930.

Figs. 31, 32 and 33 (case 5).—Section showing Betz cells described in the text. Phloxine-methylene-blue; × 930.

Fig. 34 (case 5).—Small pyramidal cells of the motor cortex showing shrinkage and hyperchromatism. Phosphotungstic acid and hematoxylin; × 930.

CEREBELLUM

The cerebella of nine monkeys were examined. Perivascular lesions were often seen in the restiform body, either spreading from the vestibular nuclei or independent of them. In the earlier cases, the roof and dentate nuclei were profusely infiltrated also, and their nerve cells were observed to be destroyed or in various stages of degeneration, although here too, many escaped damage entirely. The pericellular reaction was not marked, but focal infiltrative lesions were common, both in the nuclei and in the white matter. The Purkinje cells also showed staining abnormalities without calling forth a response from the tissue cells, but for the most part their neurofibrils appeared to be undisturbed.

COMMENT

It is not the purpose of this paper to discuss the route by means of which the virus penetrates into the nervous system, or the problems of the origin and significance of the cellular infiltrate, which have been well summarized by Hurst,[7] but rather to describe briefly the adequacy and inadequacy of the defense of the tissues against the onslaught of an infection. Unfortunately, this is an incomplete chapter in the history of the nervous system, since this description deals only with the battlefields and the early reconstruction period without stating precisely how far rehabilitation might ultimately be possible.

The period of early invasion was described by Hurst in his discussion of acute poliomyelitis.[7] Precisely what the function of the polymorphonuclear reaction to the nerve cells destroyed in the initial stages of the disease may be, remains unclear. In the light of their action as bacterial phagocytes elsewhere,[22] it is not impossible that these leukocytes bear a direct relation to the virus itself, although there is no evidence in favor of this assumption a priori. It is questionable whether they take part in the process of neuronophagia, if the situation in the nervous system is analogous to that elsewhere in the body.[22]

Neuronophagia was observed in all its various forms in the cases of the intermediate group. It was evident that the microglia acted as the sanitation unit on the tissue battlefields in that the gitter cells performed the function of carrying off cellular débris, fat and detritus to the perivascular spaces or vessels. According to Penfield,[23] the compound granular corpuscles discharge the lipoid material directly into the blood stream.

The relationship of the microglia to the various types of degeneration of the nerve cells is only partly clear. It is probable that neuronophages

22. Mudd, S.; Lucke, B.; McCutcheon, M., and Strumia, M.: Proc. New York Meeting Am. Soc. Path. & Bact., April 17-18, 1930.

23. Penfield, W.: Am. J. Path. **1**:77, 1925.

do not attack intact cells, but in the basal ganglia and brain stem, certain cells appear to be unharmed except for the proliferation of microglia cells about them. Cortical cells, on the contrary, which were thought to show pathologic changes with the routine stains, called forth no reaction on the part of the tissues. Further, the less advanced forms of microglia were not seen to contain fat. As these were in the majority, except in the destructive focal lesions of the lower levels, it is not impossible that they have a function other than phagocytosis. Since the bulk of the tissue infiltrate diminished with the process of repair, it appears likely that this, if present, is of secondary importance.

As was already evident to Levaditi and Stanesco [10] in 1910, the inroads of poliomyelitis are not only irregular in distribution but also in phase. Active lesions were found in the medulla and basal ganglia in cases in which the cervical cord showed evidence of arrest and repair. In the latter stage satellitosis replaced neuronophagia. The cortical oligodendroglia cells also appeared to be slightly increased in number, which would suggest a reparative myelin reaction.[24]

Astrocyte proliferation of a generalized type was noted in the cord and cortex, but fibrous scar formation was never observed either in the phosphotungstic acid-hematoxylin or aniline blue preparations. In the areas of destruction, the parenchymatous structure was obliterated so that not only the nerve cells but also the astrocytes were destroyed, leaving a thin meshwork heavily infiltrated with microglia cells and lymphocytes. Repair in these areas was indicated only by capillary proliferation. How far scar formation had proceeded in the cases of long duration could not be determined in the absence of gold sublimate inpregnations, but no such process was evident with the routine stains.

In regard to the perivascular reaction, the question arises whether the infiltrate may be regarded exclusively as a sign of active inflammatory activity. Doubtless the microglia cells derived from the membrana limitans gliae migrate from the vascular wall into the tissues,[7] but gitter cells laden with fat are frequently observed about the vessels as well as in the nervous parenchyma, which suggests that these cells are moving in the centrifugal current toward the spinal fluid or the blood vessels.[25] Similarly, the polymorphonuclear leukocytes that are seen in the perivascular spaces in all probability are being carried outward and eliminated, since the evidence is in favor of the theory that these cells reach the nerve tissue by penetrating the capillaries [7] and not the thicker wall of the larger vessels which they surround.

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24. del Rio Hortega, P.: Mem. r. Soc. españ. de hist. nat. **14**:5, 1928; abstr., Arch. Neurol. & Psychiat. **23**:557 (March) 1930.

25. Kubie, L. S., and Shults, G. M.: Bull. Johns Hopkins Hosp. **37**:91, 1925. Kubie (footnote 19).

In general, the intensity of the perivascular infiltrate diminishes progressively from the cord to the cortex. It is true that frequently the medulla was more affected than the cervical cords, which showed a more advanced stage of repair. Mild lesions of this type were still present in the group surviving from 242 to 309 days. Monkey 15 had apparently made a good functional recovery, and yet signs of activity persisted in the lumbar cord and in the basal ganglia.

Destruction of the nerve cells was also most evident in the spinal cords. It has been shown both here and elsewhere [7] that the virus did not act specifically on motor cells, although it may be said of both the cord and the midbrain that the anteriorly situated nuclei were most intensely involved. On the other hand, the medullary damage to the nerve cells appeared to be regional, since the sensory and motor nuclei under the floor of the fourth ventricle were attacked with equal severity, while in the basal ganglia the thalamus suffered more than the lenticular nucleus. At these subcortical levels degeneration of the neurons was frequently associated with perivascular lesions, and it was only in the cortex that, as in Hurst's acute cases, distinct disturbance occurred independently. Pathologic changes existed in the focal areas of motor or sensory cortex in which the vessels showed no inflammatory changes, although capillary increase was at times present, while neurons surrounding a perivascular cuff which did not penetrate the Robin-Virchow space often showed no more severe damage than those at a distance. The older writers referred to this type of degeneration, particularly to that of the precentral region, as "secondary." This term and its implications have been discussed by Spielmeyer [26] who pointed out that changes similar to those described in wallerian degeneration take place in many and various conditions. Were the virus carried by the blood stream, the assumption would be that penetration into the tissues occurred at the peripheral distribution of the vessel rather than along its course.

In conclusion, certain clinical application of these observations may be suggested. It is true that the infection in monkeys produced in the laboratory is far more severe than the disease in man, and it may be possible that the persistence of the lesions in human cases may be correspondingly less striking, but it seems highly probable that the process may continue to smolder long after the acute symptoms have disappeared, thus suggesting that prolonged rest may be indicated before reconstructive therapy is begun.

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26. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, vol. 1, p. 263.

SUMMARY AND CONCLUSIONS

1. Histologic studies were made of the central nervous systems of fifteen *Macacus rhesus* monkeys surviving from 19 to 309 days after the onset of acute poliomyelitis. In all cases pathologic changes were seen.

2. The type of pathologic lesions found in the acute and reparative phases of poliomyelitis corresponded roughly to the duration of the disease.

3. Inflammatory areas persisted in the central nervous systems of four animals which had made a good functional recovery.

4. A detailed study was made of the distribution and character of the lesions in the various levels of the nervous system, namely: spinal cord, spinal ganglia, medulla and pons, midbrain, basal ganglia, cortex and cerebellum.

5. These lesions have been interpreted as: (1) degenerative and inflammatory, including meningitis (negligible), perivascular and extra-adventitial infiltration, degeneration of the nerve cells and fiber tracts, and (2) reparative, including proliferation of microglia, astrocytes and capillaries.

SCHILDER'S DISEASE

REPORT OF A CASE *

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Diffuse sclerosis of the brain was first described as a disease entity by Heubner (1897). He regarded it as a disease appearing in childhood and characterized by diffuse destruction of the white matter in one or both hemispheres. Since then, many cases have been described, giving rise to detailed discussion of the character of this condition and its independent existence as a specific disease.

In 1912, Schilder [1] tried to single out and compile from the class of diffuse scleroses of the brain certain cases which he found on personal observation made up an at least anatomically well defined entity. He called it "encephalitis periaxialis diffusa," as he regarded it as an inflammation diffusely destroying the white matter, leaving the axis cylinders comparatively uninjured. According to him, the disease appears in childhood. He found it characterized by: its great extent in focal form, but with the superficial brain structure unaltered, since the cortex and sometimes the arcuate fibers are left almost entirely intact; the well defined outline of the focal area; and, histologically, an overgrowth of the glia fibers, an abundant appearance of spider cells and compound granular cells (Körnchenzellen) and perivascular infiltrates with compound granular cells and lymphocytes. The disease is, said Schilder, distinctly differentiated from tuberous sclerosis, pseudosclerosis and a number of other diffuse scleroses, and its course is subacute, exacerbating, with a slight tendency to remission, and finally fatal. However, Schilder was unable to prove any uniformity in the clinical symptom-complex, though he believed that the disease should be suspected whenever there is any sign of an extensive lesion of both hemispheres.

Since then Schilder's disease has been observed and recognized, and many cases have been reported, with descriptions of the anatomic conditions that show more or less perfect agreement with the original

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* From the Pathological Department of Karolinska Institutet, Prof. Folke Henschen, Director.

1. Schilder: Zur Kenntnis der sogenannten diffusen Sklerose (über Encephalitis periaxialis diffusa), Ztschr. f. d. ges. Neurol. & Psychiat. **10**:1, 1912.

description. In the last few years, some authors have even ventured to report cases in which there was only a clinical diagnosis. Although the disease has been regarded as so rare that every new case has been reported, it is probably commoner than has hitherto been believed, but it is not yet widely known. Julien Marie [2] suggested this possibility in 1928, and reported a collection of fifty-seven cases, most of them occurring after 1912. He also believed that this disease is the cause of a great number of neurologic and neuropsychic disorders acquired in youth. However, J. Marie was especially interested in a chronic and not fatal form of the disease that was found by the report of one case in 1913-1914 by P. Marie and Foix,[3] one in 1926 by Foix, Bariéty, Barruk and J. Marie,[4] and one in 1927 by Foix and J. Marie. This form of the disease is really the only one that has, with any semblance of general agreement, been counted as belonging to Schilder's disease; numbers of other forms, regarded as main or subordinate, have been criticized and gradually replaced by others.

Besides the cases mentioned by J. Marie, we found the following ones: Schupfer, 1902, one case (Schilder mentioned this case in 1913, but was doubtful of the diagnosis); Bullard and Southard,[5] 1905, one case; Anton and Wohlwill, 1912, two cases; Schminke, 1918, one case; Globus and Strauss,[6] 1922, one case, and 1926, three cases; Gagel,[7] 1927, one case; Urechia and Mihalescu,[8] 1927, one case. The following have been added since 1928: Kraus and Weil,[9] 1928, one case; Symonds,[10] 1928, one; Ford and Bumstad,[11] 1929, one; Leenhardt and

2. Marie, Julien: La sclérose cérébrale centrolobaire ou maladie de Schilder-Foix, Ann. de méd. **24**:545, 1928.

3. Marie, P., and Foix: Sclérose intracérébrale centrolobaire et symétrique, Rev. neurol. **25**:346, 1913; **27**:1, 1914.

4. Foix; Bariéty; Barruk, and Marie, J.: A propos d'un nouveau cas de sclérose intracérébrale centrolobaire et symétrique, Rev. neurol. **1**:930, 1926.

5. Bullard and Southard: Diffuse Glioses of the Cerebral White Matter in a Child, J. Nerv. & Ment. Dis. **33**:188, 1906.

6. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy (Schilder's Disease), Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

7. Gagel: Zur Frage der diffusen Sklerose, Ztschr. f. d. ges. Neurol. & Psychiat. **109**:418, 1927.

8. Urechia and Mihalescu: Quelques remarques sur un cas de sclérose périaxiale, Rev. neurol. **2**:101, 1927.

9. Kraus and Weil: Encéphalite périaxile diffuse (type Schilder), Encéphale **23**:775, 1928.

10. Symonds: Encephalitis Periaxialis Diffusa; Schilder's Encephalitis: A Critical Review, Brit. J. Child. Dis. **25**:83, 1928; Contribution to Clinical Study of Schilder's Encephalitis, Brain **51**:24, 1928.

11. Ford and Bumstad: Encephalitis Periaxialis Diffusa of Schilder: Report of Two Cases with Anatomical Findings, Bull. Johns Hopkins Hosp. **44**:443, 1929.

Chaptal,[12] 1929, one; Schelden, Doyle and Kernohan,[13] 1929, two cases; Austregesilo, Gallotti and Borges,[14] 1930, one.

We have not included cases diagnosed clinically without substantiation by anatomic examination. To be sure, Leenhardt and Chaptal gave only a clinical report of their case, but they inspected the brain grossly and found support for the diagnosis. We believe with Symonds, among others, that such inspection may be sufficient, and have therefore included this case. With J. Marie's material, the number of cases reported is thus about seventy-five. However, in accord with Marie, we wish to point out that many of these cases are disputed; some are, by the majority of authors, denied a place among the cases of Schilder's disease.

REPORT OF CASE

Clinical History.—A boy, aged 6½ years, whose parents and siblings were all healthy and in whose family, as far as is known, there had been no nervous diseases, was born two weeks before full term. He was said always to have been ailing, whimpering and nervous, and to have had a poor digestion and frequent insomnia, though he had no actual disease until December, 1928, at which time he had a mild case of influenza. In February, 1929, both he and the other children were ill for three or four weeks. He had fever and pain above the eyes, and slept unusually much, but was fully awake and lucid in the intervals. The disease was diagnosed by the physician as influenza. The patient became much better, and was sent to the country for convalescent treatment. In May, it was found that he was beginning to be apathetic and slow in carrying out actions; at the end of June, his legs became weak and he stumbled in walking; speech at the same time became thick, and hearing was impaired. In July, he had a few convulsive seizures affecting the whole body without loss of conciousness, and the motions of the hands were fumbling. He did not have fever or headache and did not vomit.

Examination on Admission to the Sachs Children's Hospital in August, 1929.—The child was physically well developed, with no symptoms except those referable to the nervous system. He presented a picture of apathetic dementia; a languid and indolent appearance of the face, with the mouth half open, and sluggish changes of expression. He understood and carried out commands imperfectly.

Cranial Nerves: The patient was plainly able to see, and looked in different directions, though sometimes with imperfect coordination. However, there did not seem to be any paresis of the ocular muscles. He reacted to pricking of the skin. The corneal reflexes were normal. There was no genuine paresis of the facial nerve. The patient was able to wink the eyes and smile slightly. There was a paramimia. The galvanic reaction in the facial nerve was normal. There was no paresis of the tongue or palate. Hearing was extremely reduced. The patient did

12. Leenhardt and Chaptal: Triplégie spastique, crises d'épilepsie souscorticale et déchéance psychique; encéphalite périaxile diffuse (type Schilder), Gaz. méd. de France **3**:195, 1929.

13. Schelden, W. D.; Doyle, J. B., and Kernohan, J. W.: Encephalitis periaxialis diffusa, Arch. Neurol. & Psychiat. **21**:1270 (June) 1929.

14. Austregesilo, Gallotti and Borges: Leucoencéphalopathie diffuse (maladie de Schilder), Rev. neurol. **1**:1, 1930.

not understand words, but had auditory reflexes, reacting to loud sounds with starts and winking. He spoke little, saying only isolated words, though with a fairly distinct enunciation. The left pupil was somewhat more dilated than the right; there was a sluggish reaction to light.

The ocular fundi were normal; there was no papillary stasis (the fundi were reexamined repeatedly, but were always found to be normal).

Trunk and Extremities: The patient reacted all over the body to pricks. No other test of sensibility could be made because of the patient's psychic condition. There was paresis of the arms without intensified tendon reflexes. A slight ataxia was present in the arms. There was spastic paresis in both legs. No pronounced abdominal paresis was observed. The patient was able to rise to a sitting position. Babinski's reflex was positive bilaterally. No abdominal reflex was elicited.

Spinal Fluid: On August 3, examination showed: pressure, 10 cm.; clear fluid; Queckenstedt test, normal readings; Nonne test, +; Pandy test, ++; 7 cells per cubic millimeter, all lymphocytes; Wassermann test, negative.

On August 20, there was no rise in the manometer tube; the lymphocyte count was 72; Nonne test, +; the Pandy test, +.

On October 16, examination showed: pressure, 10 cm.; clear fluid; Nonne test, +; Pandy test, +; 1 cell per cubic millimeter.

On October 26, examination showed: pressure, 12 cm.; clear fluid; Nonne test, —; Pandy test, —; no cells.

Other Laboratory Data: Tests with tuberculin, up to 2 mg. given subcutaneously, gave negative results. On August 3, the sedimentation reaction was 7 mm. in one hour and 16 mm. in two hours.

Roentgenograms disclosed a large and exceedingly thin cranium, but no visible rupture of the sutures or calcifications.

On September 10, the caloric reaction in both ears was normal. Trömner's test was positive in both hands.

Course.—There was a slow exacerbation of the symptoms. At the end of August, the patient was still able to walk with support, though with great difficulty. He made simple, imitative motions. He was able to smile, and knew the names of ordinary objects, such as cloth, ball, etc., but had difficulty in pronouncing them, which troubled him and caused him to shake his head. During the entire illness, he was unable to retain the urine and feces.

On September 15, the following comments were written: The patient presents a general psychic dementia indicating an extensive injury to the cortex. There are undoubted symptoms from the pyramidal tract, strongest in the lower extremities, weaker in the upper ones (increased reflex excitability with clonus and a positive Trömner test), corresponding to a hemispheric lesion. As there are auditory reflexes (the patient starts on hearing loud sounds) and the vestibular nerves react normally, the disturbance in hearing can probably be located above the nuclei of the pons. There is no definite facial paresis, but there is a rigidity in the expression of the face, a paramimia, due probably to injury to the basal ganglia. The ataxia and general rigidity may also be referred to these, leaving no symptoms of a disease of the pons as was first suspected. The disturbance in speech cannot be definitely accounted for (possibly it is secondary to the reduced hearing, or due to a motor aphasia). The lack of symptoms of pressure and papillary stasis argue against the presence of a tumor. The possibility of tuberculosis may be excluded (a negative tuberculin test). The increase of cells and the positive protein reaction in the cerebrospinal fluid indicate an inflammatory process. The considerable extent of the process, the age of the patient, the slow progress of the disease and its latent start with no known antecedents argue rather

strongly against multiple sclerosis, though an acute attack of this disease is not out of the question. There is no reason to suspect syphilis (a negative Wassermann reaction). Although the course of the disease has been unusual, irrespective of whether it had its onset in February, followed by an interval of health lasting three months, or in May with disregarded acute symptoms, the probable diagnosis is extensive subacute encephalitis (of a nonlethargic type) with its location in the cortex or the white matter, and with an unfavorable prognosis. The further progress of the disease substantiated this opinion.

In September and October, the patient was given six intravenous injections of neoarsphenamine, from 0.06 to 0.09 Gm. each, without effect. Beginning with November 13, intramuscular injections of "sulphosin" were given for the purpose of inducing fever; without these injections, the temperature had from the start been between 37.4 and 37.9 or 38 C. (99.3 and 100.2 or 100.4 F.). Four injections in all were made, varying from 0.25 to 1 cc. After each injection the temperature rose to 40 C. (104 F.), and rapidly sank again. On November 24, after the injection, the patient had a severe reaction, with great restlessness, redness of the face, intense perspiration, a temperature of 40.5 C. (104.9 F.), a fluttering pulse, 300 per minute, and superficial breathing.

During the last two months, the patient gradually became more out of touch with the world; he had an expressionless glance which never focused on anything, and recognized no one around him. The general rigidity and spasticity varied somewhat, but increased, and the patient lay as stiff as a log in bed. On being touched, he gave vent to inarticulate cries. He was fed mostly through a tube. The pupils were moderately dilated and did not react to light. There were athetoid movements of the fingers. The Babinski sign was fluctuating, and occasionally negative. There were no symptoms from the medulla oblongata. The temperature during the last two weeks fluctuated around 38 C., and the patient died after a sudden, spontaneous rise to 41 C. (105.8 F.), accompanied by symptoms resembling those that had appeared after an injection of sulphosin, with no signs of pneumonia or other infection.

Postmortem Examination.—At the autopsy, performed by Prof. F. Henschen, only the cranium and part of the spinal canal (the cervical and lumbar parts) were opened. The cranial bones were rather thin. There was a pronounced hyperemia of the meninges. Edema was present in the pia-arachnoid membrane, which was possibly somewhat thicker at the base.

There was a pronounced hyperemia of the brain and spinal cord. The brain was symmetrical. The gyri and sulci had a normal structure. Frontal section through the brain revealed that the white matter was the seat of a pathologic process occupying the greater part of the occipital, temporal and parietal lobes and part of the frontal lobes, and involving as well the basal ganglia and the internal and external capsules. The foci were made up of confluent areas of a grayish-white to a pale yellow, partly transparent color, which near the periphery merged into a hyperemic zone with a muddier, grayish-brown appearance. The cortex apparently was intact, the focal areas being separated from it by long streaks of thin, white medullary substance, barely 1 mm. across. The consistency of the foci was exceedingly firm, like rubber, but in the peripheral parts it was soft, in some spots even softer than usual, with a tendency to fall apart on being cut. The affected areas left intact the anterior parts of the basal ganglia, and there extended laterally to them in the shape of a thin disk along the floor of the insula. In the sections of the anterior frontal lobes there were several smaller, rounded, apparently isolated foci with a fresher appearance, but sections from adjacent areas proved that these were branches from the main foci.

In the cerebellum there was also a large focal area, symmetrically filling practically all the white matter. Sections through the pons and medulla oblongata revealed the pyramidal tract slightly shrunken, with a drab, grayish color.

Microscopic Examination.—Myelinic Changes: The disappearance of myelin is characteristic of the disease. This is variously described in different cases.

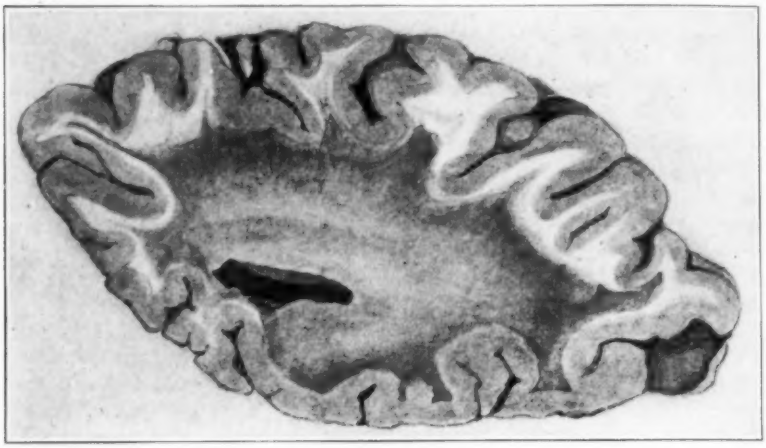

Fig. 1.—Extent of the focal area in a frontal section through the right hemisphere.

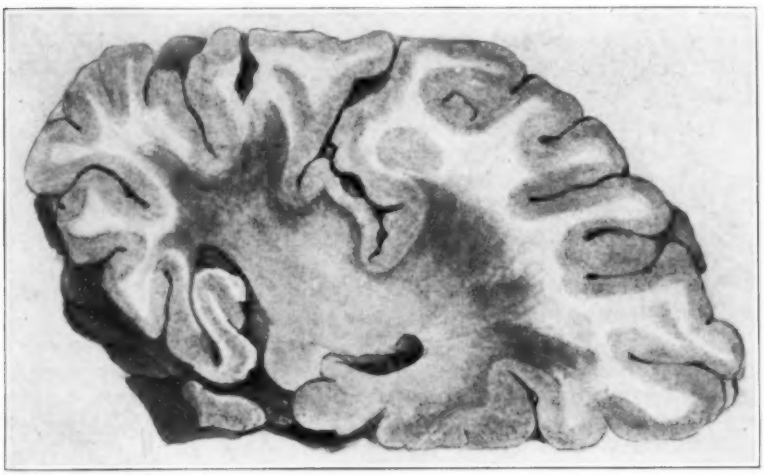

Fig. 2.—Extent of the focal area in a frontal section through the right hemisphere.

Usually there is a diffuse dissolution throughout a large focal area spreading continuously in every direction. Sometimes, however, there is reason to suppose that the process develops through the confluence of multiple, small, isolated foci which have thus formed a single large focal area. Many authorities oppose this inter-

pretation of the spread of the process, attaching great importance to the presence of small foci, particularly in consideration of the disease known as multiple sclerosis, which has hitherto as a rule been sharply differentiated from Schilder's disease, and is typified by this manner of spreading. In the opinion of these authors, the presence of many small foci indicates a diagnosis of multiple sclerosis. In some cases, the authors maintained that there was localized destruction around the vessels. Krabbe,[15] in particular, went so far as to call the disease "perivascular myelin necrosis." However, he later abandoned this view,[16] and we think that the general opinion at present is that the lesion is continuous. Bouman[17] was among those to support this opinion, in opposition to Marburg's[18] alleged observation that the lesion in multiple sclerosis is not continuous. Since Schilder's disease is not sharply distinguishable from multiple sclerosis, however, the continuity of the lesion cannot be regarded as characteristic, particularly as small, isolated, well defined foci sometimes are present as well as the large focus. It is often pointed

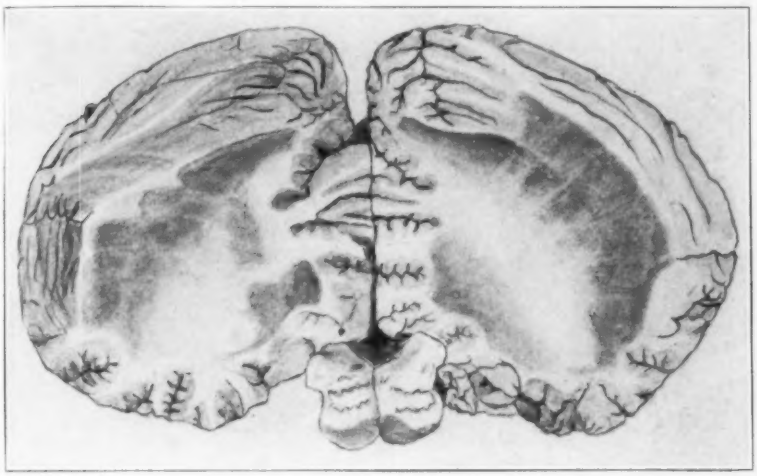

Fig. 3.—Extent of the focal area in the cerebellum.

out as a typical feature of the disease that in demyelinization the arcuate fibers are preserved in a narrow border along the cortex, and that except in a few unusual cases the cortex itself is entirely untouched by the process. Nevertheless, the arcuate fibers are affected in most cases, and a focus in the cortex was

15. Krabbe: Beitrag zur Kenntnis der Frühstadien der diffusen Hirnsklerose (die perivasculäre Marknekrose), Ztschr. f. d. ges. Neurol. & Psychiat. **20**:108, 1913.

16. Krabbe: A New Familial, Infantile Form of Diffuse Brain Sclerosis, Brain **39**:74, 1916.

17. Bouman: Encephalitis periaxialis diffusa, Brain **47**:453, 1924. Brock, S.; Carrol, P. M., and Stevenson, L.: Encephalitis periaxialis diffusa of Schilder, Arch. Neurol. & Psychiat. **15**:297 (March) 1926.

18. Marburg: Die sogenannte "akute multiple Sklerose" (Encephalomyelitis periaxialis scleroticans), Jahrb. f. Psychiat. & Neurol. **27**:211, 1906; Handb. d. Neurol. **2**:911, 1911.

described by Schilder himself in 1912. In most cases, however, the process must be regarded as a demyelinization affecting mainly the white matter and usually definitely limited by the cortex. The focal area may stretch far down into the internal capsule and more or less affect the basal ganglia. Large areas lacking myelin and having no connection with the main focal area have also been found in the cerebellum and the pons, and occasionally even in the spinal cord.

In our case, there was complete destruction of the myelin in the large foci in both hemispheres. After myelin staining, these areas looked entirely colorless. The destruction of the myelin had taken place in most of the white matter of the occipital, temporal and parietal lobes and the posterior part of the frontal lobes.

Fig. 4.—Section from the right temporal lobe. Dissolution of myelin. Arcuate fibers partially intact. Spielmeyer's myelin stain.

It extended all the way out to the cortex in several places, down into the internal and external capsules and into the basal ganglia.

There was also a large focus in the cerebellum symmetrically occupying the greater part of the white matter in both hemispheres. The arcuate fibers were intact for great distances. Here and there, however, the process reached all the way to the cortex, and the radiating fibers appeared to be reduced in number. The transition from normal to altered areas is not sudden. The transitional area is narrow, it is true, and may therefore be regarded as a fairly well defined boundary; but within it, the destruction of the myelin can be seen to go on gradu-

ally from slightly affected fibers to pronounced dissolution. The fibers become fewer, are winding, and have an irregular course showing every phase to complete disintegration in the shape of bulbar inflation, rosary forms and balls or fragments of different sizes lying isolated or in groups. Among these, comparatively uninjured fibers can be seen winding around cells of which a large number have a bluish shade and others are colorless (Spielmeyer's stain).

In a thick section, bordering on the area of myelin destruction, we could see the mass of myelin punctured by numerous small holes, most of them apparently empty, some of them representing vessels and others cells (in a specimen with the Spielmeyer stain visible only after diaphragming) with the protoplasm large

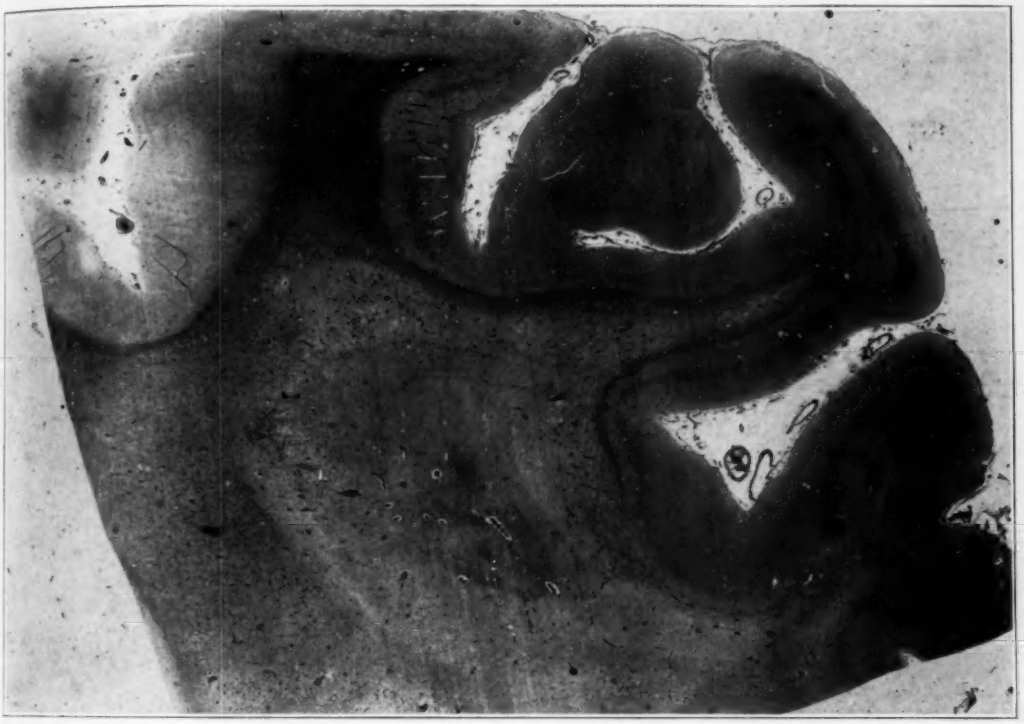

Fig. 5.—Section from the right occipital lobe. Fissura calcarina. Dissolution of myelin. Arcuate fibers intact. Iron hematoxylin stain.

and colorless, either isolated or in groups of two or three. The nucleus was small, pyknotic and often excentrically located, and the protoplasm was not homogeneous but cloudy and granular with an indefinite outline. These cells were also visible in specimens stained with iron hematoxylin or Bielschowsky's stain. Around the holes, the fibers sometimes appeared dislocated, but a few passed straight through and looked either entirely normal or swollen. As mentioned, these holes were found only near the large focal area, but there were no signs of any myelin destruction advancing in their periphery; the transition was made by diffuse degen-

eration of all the fibers. Schaltenbrand [19] described the development of holes in the transition to the destroyed tissue, which he found to be deposits of mucin. With this in mind, we made a mucicarmine stain, but obtained no positive result. In our case, the holes plainly represented degenerate fibers partially replaced by phagocytes and becoming plainly visible when the section struck the focus more or less tangentially. On the other hand, we saw no large, isolated foci with complete dissolution of the myelin, either around the vessels or elsewhere, that could be thought to be primary degenerative foci from which the largest focus might have developed by confluence. Within the demyelinated areas, an occasional normal myelin fiber was sometimes found, to our surprise, or there might be isolated

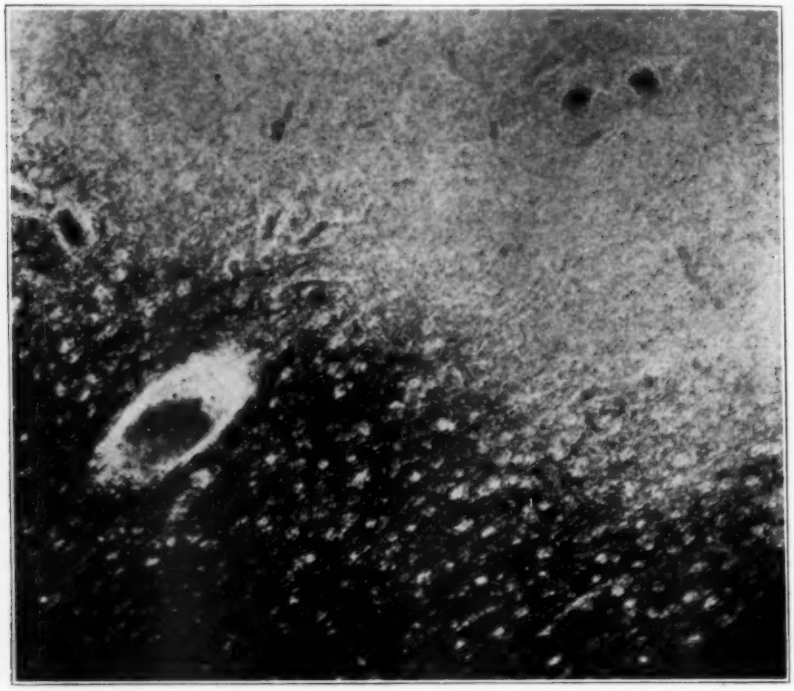

Fig. 6.—Transitional area between normal and pathologically changed parts. Spielmeyer's myelin stain.

groups of unconfigurated lumps of different sizes which took the myelin stain and were evidently made up of free myelin droplets in the tissue.

In the cerebellum, too, the focal areas left the cortex intact. In a narrow seam around the nuclei dentati the fibers were fairly well preserved, but in a few places the process appeared to penetrate between the nerve cells with dissolution of myelin and massing of phagocytes. In the pons, the medulla oblongata and the spinal cord, only the pyramidal tract was entirely without myelin, and in the lumbar region, both the crossed and the left direct tract.

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19. Schaltenbrand, G.: Encephalitis periaxialis diffusa (Schilder), Arch. Neurol. & Psychiat. **18**:944 (Dec.) 1927.

The focal area itself and the secondary degenerated parts may present great similarities, as Schaltenbrand also pointed out. He even expressed the belief that the histologic picture is insufficient for differentiation both from multiple sclerosis and, to some extent, from secondary degeneration. However, when the process proves to be strictly limited to a certain tract, as in our case, the difference should be clear.

Axis Cylinders and Nerve Cells: According to Schilder the axis cylinders are immune, but only comparatively so. In support of this opinion, it has been pointed out that one may find in the heart of a focal area not only apparently intact axis cylinders, but also undoubtedy disintegrated ones. Other observers have found them

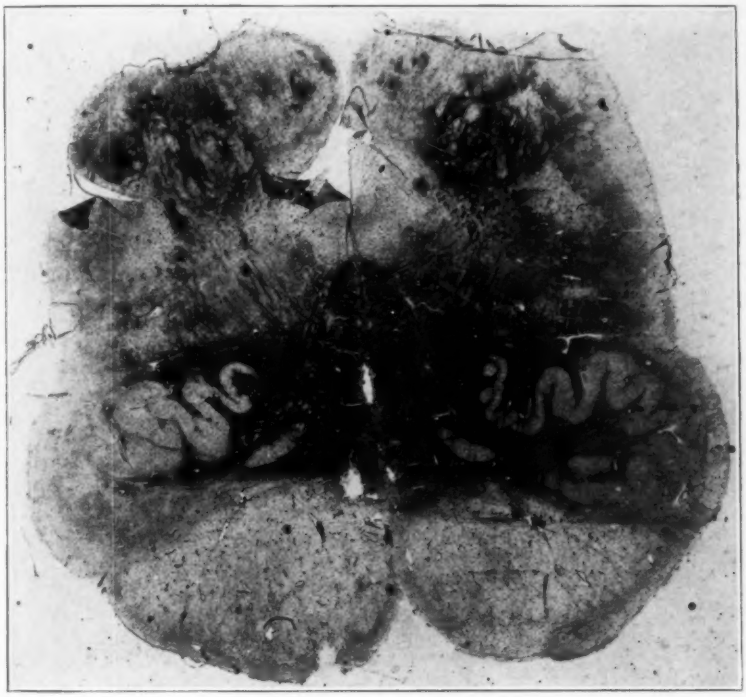

Fig. 7.—Medulla oblongata. Degeneration of pyramidal tract. Spielmeyer's myelin stain.

more or less affected, even to the point of parallelism between dissolution of myelin and that of axis cylinders (Walter, Jakob).

In our case, there were great changes in the axis cylinders, on the whole keeping pace with those of the medullary sheaths. In the heart of the focal areas, the axis cylinders had practically disappeared, though one or two of them with a normal appearance might be found, as in the case of the medullary sheaths. Near the periphery there were numerous fragments of axis cylinders, as well as decidedly affected, swollen and winding stumps which frequently terminated in a rounded or spoon-shaped thickening. The boundary between the normal and the pathologic areas was not as near the periphery in the case of the axis cylinders as in that of the medullary sheaths. It was not sharply defined, but was expressed

by a diffuse attenuation which nearer the center presented a spotty, uneven transition into the area of complete dissolution. While the destruction of myelin was accompanied at its outer limits by perivascular massing of cells, the axis cylinders were found deep in among the altered vessels in thin, winding bundles, separated or compressed by the phagocytic glia cells or the dilated vascular spaces. From the general picture, the conclusion may therefore be drawn that both the medullary sheaths and the axis cylinders are to a large extent destroyed in this disease. However, the axis cylinders appear to be somewhat more resistant. In estimating the resistance of the axis cylinders as compared with the medullary sheaths, it might be suitable to make a comparison of the clinical symptoms and the extent of the injury as judged from a myelin-stained specimen. This, it must be admitted,

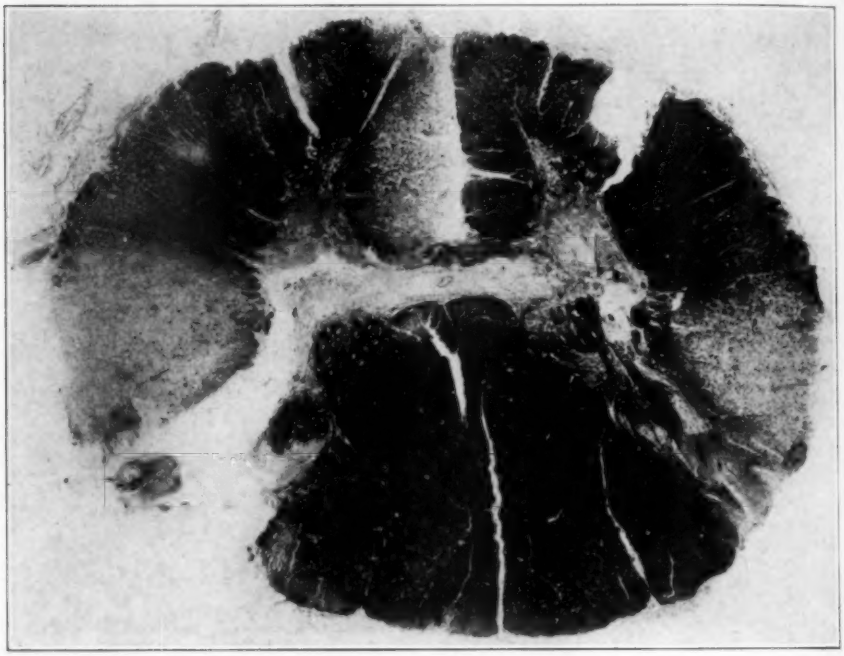

Fig. 8.—Section of cord at level of first thoracic vertebra. Degeneration of the crossed and the (left) direct pyramidal tract. Spielmeyer's myelin stain.

is difficult, as the process is so extensive that a more deeply located necrosis may be the cause of the symptoms that one is trying to account for by the extent of the changes on a superficial area. Finally, the comatose and difficult final stage of the disease greatly hinders a precise clinical localization to be compared with the histologic picture. In this case, however, it does seem as if the destruction of the axis cylinders on the whole was commensurate with the extent of the focal area, for which reason we may say that there was a certain clinical correspondence in the symptoms. That the axis cylinders or the ganglion cells were injured was obvious in this case at a very early stage, but whether the injury was cortical or subcortical is more difficult to determine. One hardly expects to find by microscopic examination any pronounced disease of the cortex when it has appeared to

be intact on macroscopic inspection. There are various reports in the literature on lesions of the cortex. Isolated foci involving the cortex have been described in several cases, but one of the characteristics of the disease is supposed to be the subcortical lesion. A few authors mention atrophy of certain layers of cells, with symptoms of irritation and acute alteration in the ganglion cells, deposition of fat, tigrolysis, destruction of the fibers, swelling, etc., but even when this was found, authors have attached little importance to it, and have pointed out that such changes may also be found in normal brains; hence it is wise to be conservative in judgment. As far as we know, no thorough examination has ever been made of the cell layers or cells in normal brains, with the exception of certain nuclear groups and limited cortical areas, for the purpose of discovering to what extent these alterations are pathologic. In our case, no great importance was attached to the results of the examination of the cells except when the changes were obviously connected with the extent of the injury, particularly in the case of the

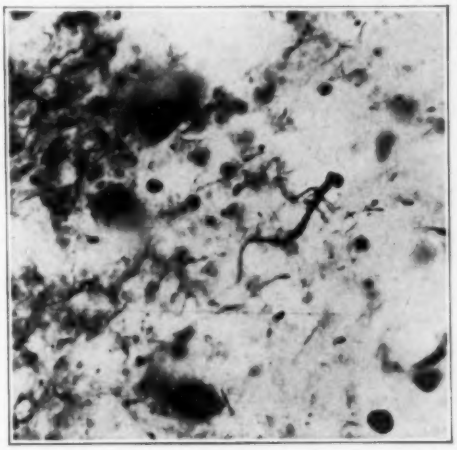

Fig. 9.—Section from left internal capsule. Axis cylinders greatly reduced in number, the remaining ones plainly affected. Bielschowsky stain.

basal ganglia, although the latter are subject to great changes even in a normal brain.

The cortex was in the main intact. In a few places in which demyelinization extended up to the cortex and even the arcuate fibers were affected, we found that the fifth and sixth layers were somewhat thinner and more deficient in cells than adjacent areas. Nowhere, however, did the process penetrate the cortex deeply. Isolated cells in the remaining layers of the cortex were indeed altered (swelling, tigrolysis, dislocated nuclei, small fat droplets), but whether to a greater extent than normal is doubtful.

In the basal ganglia great changes accompanied the extension of the focus into the internal and external capsules, with deformity and depressions in the normal structure, particularly of the globus pallidus and the thalamus, but also of parts of the nucleus caudatus, the putamen and the claustrum. At some distance from the foci, the nerve cells were essentially unaltered, but close to the foci we saw in practically all the cells pronounced signs of irritation up to complete destruction,

as well as numerous areas of neuronophagia. This is, of course, an explanation of the clinical symptoms of a disease of the basal ganglia (paramimia, athetosis, general rigidity, etc.).

In the cerebellum, in which a large focus serves to explain the patient's ataxia, there was no definite disease of the cortex. The nuclei dentati in both hemispheres were partially involved in the process, showing pronounced changes in the nerve cells.

In the pons, the medulla oblongata and the spinal cord, there were no definite changes with the exception of degeneration of the fibers in the pyramidal tract, paralleling the destruction of myelin.

Glia: The glia has been made the subject of extensive special study by several authors who have been studying Schilder's disease. They found that all the glial

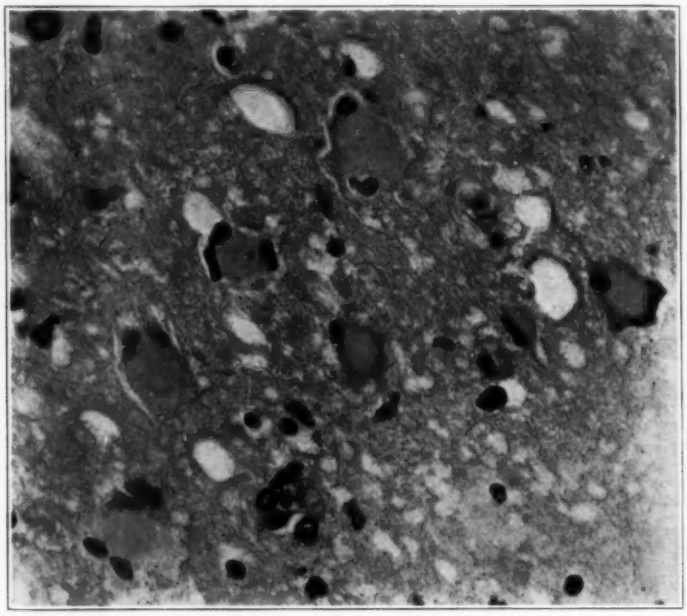

Fig. 10.—Globoid cells. Hematoxylin eosin.

elements take part, to a greater or lesser extent, in the process. In the study of our case, we used only Holzer's neuroglia stain.

The focus is recognizable by a wall of dense glia elements, varying in appearance according as the process is of an older or more recent date. The microglia is represented above all by the gitter cells ("Körnchenzellen," "scavenger" or "compound granular cells"). Schaltenbrand in his case found transitional forms from typical microglia to rod cells, and from these to gitter cells. We cannot with certainty say that we have encountered any such transitional forms, though each of these types of cells probably was present. The gitter cells were scattered throughout the entire pathologically altered tissue, but were few and smaller in the older parts of the focus and in these places, as a rule, were grouped around the vessels. In the more recently developed parts of the foci, in which the process was evidently still spreading, almost all the cells were gitter cells; there were a few

multinucleated glia cells of the astrocyte type. In the older parts, on the other hand, the neuroglia was predominant and consisted of fiber-forming astrocytes, the fibers of which became gradually thinner toward the center of the focus, but also more numerous, forming an enormously dense isomorphic or anisomorphic felt-work of glia fibrils. Like Spielmeyer,[20] who described the transformation of the astrocytes in older foci in multiple sclerosis into fibers at the cost of the protoplasm, we also found that the nuclei were fewer, the individual ones either pale and large, lying isolated, or dark and small, one or two together surrounded by a fine seam of plasma which appeared to be almost entirely filled with fibrils running

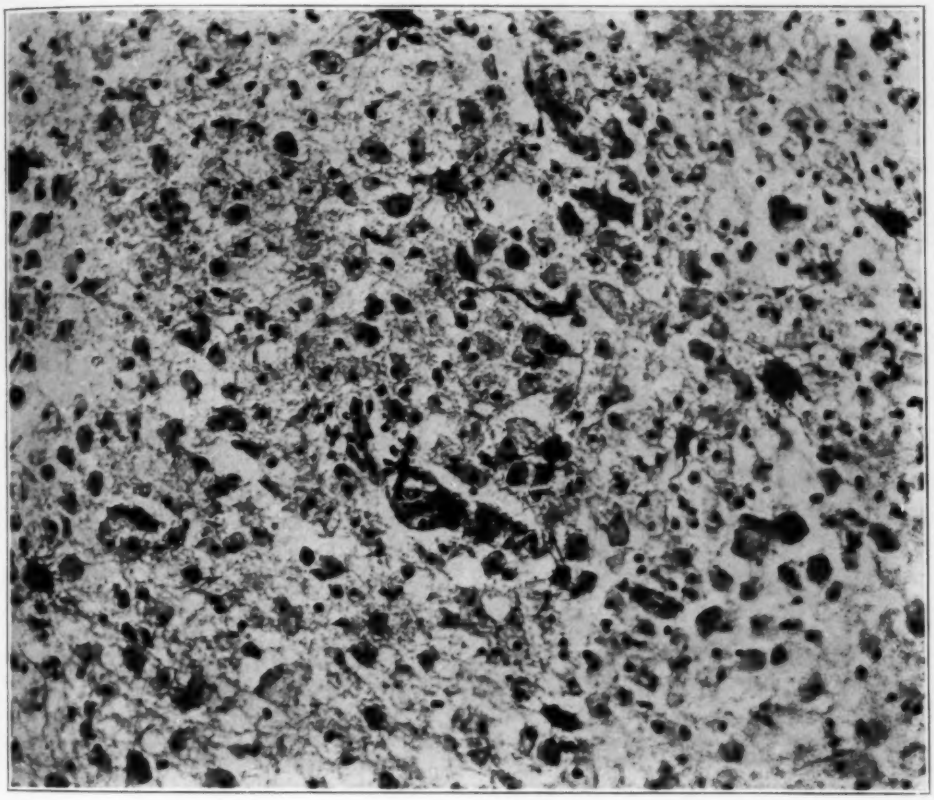

Fig. 11.—From the periphery of the focus. Holzer's glia stain.

through several cells. In the transitions to more recent focal areas, there were larger masses of protoplasm with from two to four nuclei in the periphery, and shorter, coarser fibers. Sometimes there were transitional forms having a large, homogeneous, occasionally vacuolated protoplasm with a varying number of nuclei of different sizes which were regularly located in the periphery, were elongated and irregular in shape, and sometimes protruded from the cell and simulated gliophagia. Sometimes, they had isolated pyknotic nuclei, in which case the cell outline was indistinct.

20. Spielmeyer: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, vol. 1.

These cells, "gemästete Glia" (Nissl) or "globoid cells" (Collier and Greenfield), have been the subject of lively discussion. Some authors considered them pathognomonic of Schilder's disease (Collier and Greenfield[21]), while others pointed out that most of them much resemble cells found in tuberous sclerosis of the brain and in Westphal and Strümpell's pseudosclerosis. We think it most likely that these globoid cells constitute a regressive alteration of the astrocytes (Schaltenbrand and others), but that they are by no means specific in Schilder's disease. This implies, too, that they are cells with a regenerative function (Barré; Morin; Draganesco and Reys[22]), expressed by their tendency to form fibers in

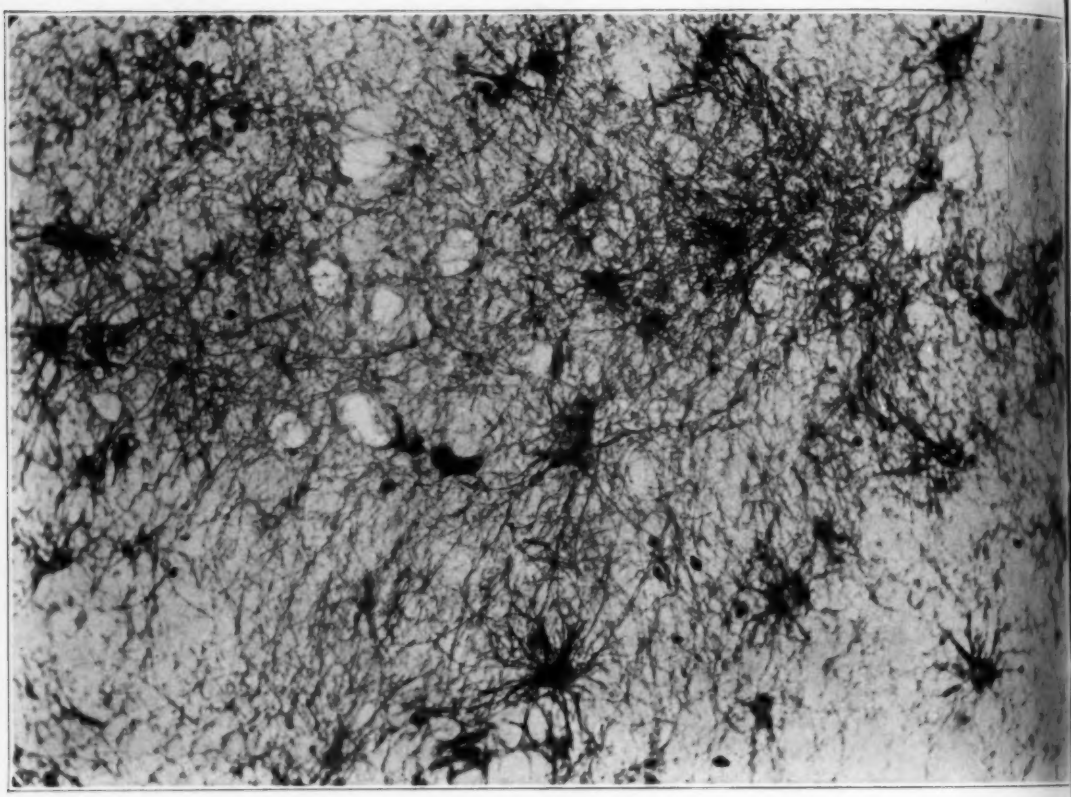

Fig. 12.—From the center of the focus. Holzer's glia stain.

the older areas in which they are the typical astrocytes. Collier and Greenfield saw no fibers on their globoid cells, but they stand alone in this observation. J. Marie, who in accord with Foix called these cells "cellules pseudogliomateuses," found fibers and thought it possible that the cells were the same as Collier and

21. Collier and Greenfield: The Encephalitis Periaxialis of Schilder: A Clinical and Pathological Study, with an Account of Two Cases, One of Which Was Diagnosed During Life, Brain **47**:489, 1924.

22. Barré, Morin, Draganesco and Reys: Encéphalite périaxiale diffuse (Type Schilder): Syndrome tétraplégique avec stase papillaire, Rev. neurol. **2**:541, 1926.

Greenfield's, but appearing in two different forms. In our case we found no globoid cells that definitely lacked fibers; with practically all the stains used (hematoxylin-eosin, iron hematoxylin, van Gieson's, Nissl's and Holzer's), we found fibers, though they were sometimes no more than a plasmatic fringe.

Schilder's opinion that these cells have a phagocytic function cannot be entirely rejected, as numbers of them are occasionally seen in the transitional zones with well preserved nuclei and distinct outlines, and containing more or less fat; rarely, they are also present in the dilated vascular spaces. However, some of these fat-

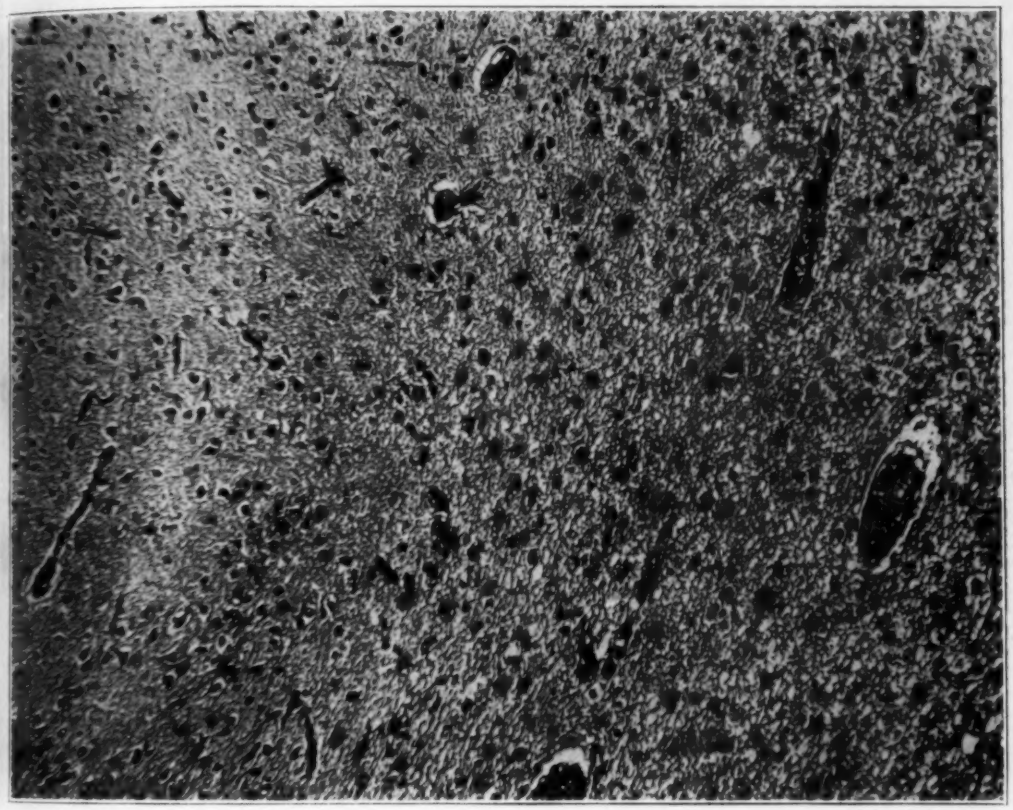

Fig. 13.—Older part of the focus with gliosis. Cortex intact. Iron hematoxylin stain.

containing globoid cells present undoubted signs of degeneration in the shape of pyknotic nuclei, disintegration and protrusion of the protoplasm; this cannot be interpreted as a sort of ameboidism or an artificial result of cutting, as they were found almost exclusively in the transitional zone. Substantially, these changes must be degenerative, a supposition supported mainly by the morphologic transition from the large, fat-free fiber-forming astrocytes to the globoid cells containing more or less fat and an increased number of nuclei, and with fibers that have partially lost their stainability.

Ferraro [23] found globoid cells taking a myelin stain, as well as "myelin bodies" without nuclei, but otherwise morphologically resembling ordinary ones, particularly in the transitional areas in which there were still some medullary sheaths. In our case, we also saw cells, sometimes numerous cells, and bundles taking a pale myelin stain. As a rule, however, it was possible after diaphragming to distinguish them as cells of the gitter cell type. We saw no globoid cells taking this stain.

In connection with the globoid cells, we may mention certain cells that we observed in the transitional zones between areas of older and more recent alteration, cells that we regard as fitting fairly well Spielmeyer's description of "Alzheimer's Gliazellen" in Westphal and Strümpell's pseudosclerosis. They have an enormous, pale nucleus with a distinct nucleolus and are unevenly sprinkled with chromatin, which in a few cells is not limited to the nucleus but can also be seen in the surrounding protoplasm as bluish-black grains (Holzer's stain). The nucleus varies from round to kidney-shape, or is irregularly elongated, but as a rule it is oval. Occasionally, one sees nuclei that appear to be in the process of division, but this is most commonly in cells that show rather close relationship with the globoid cells. The protoplasm is frequently homogeneous in appearance, and may be pale and not easily discovered, so that the nucleus looks as if it were lying isolated in a rounded, paler field. As a rule, however, it is possible to see the protoplasm, which has short thick protrusions without fibrils. At the edges of the feltwork, the fiber-forming glia has a tendency to develop a dense lattice around the vessels.

With regard to the consistency of the brain, various authors have made different assertions. In some cases the consistency was greatly diminished, almost to liquefaction, and in others extremely increased, but these conditions were dependent on the more or less acute progress of the disease in the different cases. In cases of long standing there was a considerable increase of the glia fibers with consequent hardening of the brain, and in the more recent cases there was the opposite condition. In our case, the different parts of the brain varied in consistency according to the structure of the glia. Thus, the outer edges of the focal area were soft and the older, fibrous parts firm and elastic.

In the areas of secondary degeneration we also found gitter cells and globoid cells, though they were much less numerous here than in the primary focus.

Fat: With fat staining (sudan III, scarlet R) it was possible, even with the naked eye, to see a red outlining of the focus like a wall, with the central part comparatively pale and the periphery deep red and passing diffusely into the yellowish shade produced by intact myelin substance, but sharply distinguished from the cortex. The older parts of the focal area were thus apparently entirely free from fat.

Under the microscope, one first sees in the adjacent cortical regions isolated fat phagocytes, either free in the tissue or more frequently in the adventitial spaces, which were here only moderately dilated. These fat phagocytes are all of the gitter cell type, containing globules of different sizes, usually bright red or orange, which sometimes occupy the entire protoplasm of the cell but more commonly only a part of it. In the transition to the altered areas, the fat phagocytes become more numerous, sometimes even in the fifth and sixth cortical layers, and in the peripheral parts of the focus they make up practically all of the free cell elements. The genuine fat phagocytes here consist of gitter cells with their

23. Ferraro: Familial Form of Encephalitis Periaxialis Diffusa, J. Nerv. & Ment. Dis. **66**:329, 1927.

large, granular protoplasm and small, dark nuclei, the latter sometimes centrally, but more often excentrically, located. However, some gitter cells in this transitional region do not take the fat stain, and these correspond in number and grouping with the cells already mentioned as showing an affinity for the myelin stain. Here there are also globoid cells with their large and sometimes spotted granular, but more often homogeneous, protoplasm framed by from two to six irregularly shaped nuclei of different sizes, and many of these cells, too, contain globules of fat.

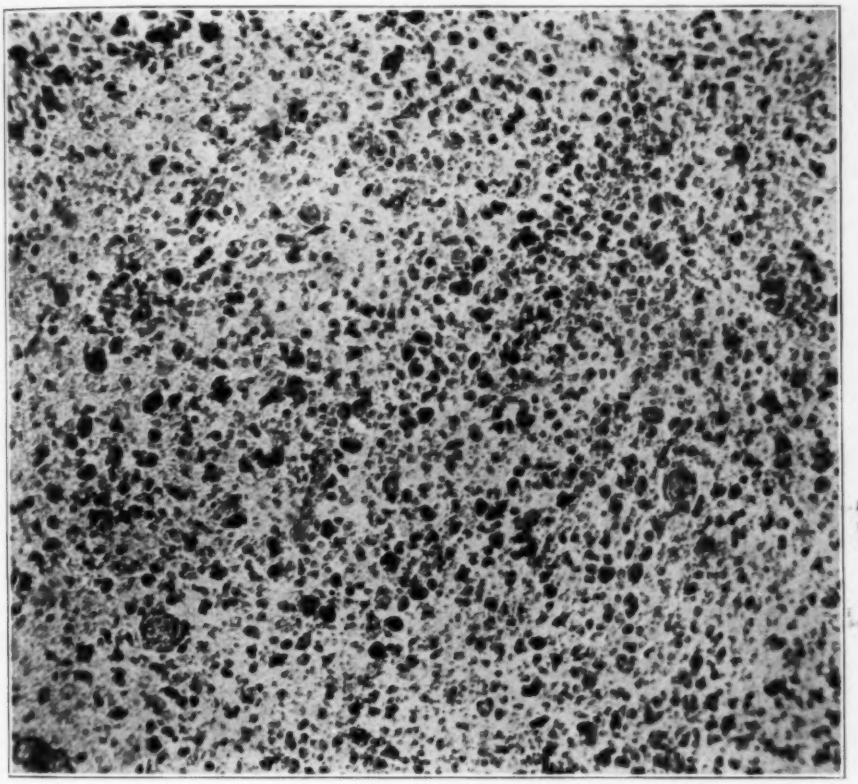

Fig. 14.—From the periphery of the focus. Numerous fat-bearing cells. Scarlet R stain.

In the transitional areas, the dissolution of myelin was directly proportionate to the appearance of gitter cells, crammed with fat, scattered diffusely in the tissue. Nearer the interior of the foci they have a tendency to gather around the vessels and sometimes mass layer on layer in the considerably dilated adventitial spaces. However, it seems as if several of the cells had relinquished their fat content; the number of fat globules in them had diminished or entirely disappeared, they become smaller, and the protoplasm is denser and takes on a more compact stain shading into brown. The endothelial cells in the vessels also occasionally contain fat. Still closer to the center, the process takes on the appearance

of scar formation with pronounced proliferation of the glia fibers, and here there is very little fat; what there is occurs only as isolated globules in the periphery of the astrocyte protoplasm, in an occasional gitter cell or in the cells that are present to only a slight extent around the vessels. The distribution is everywhere as already described.

It is of special interest to see that the ependymal cells also play a part in the resorption of fat. The ependymal layer contains a large amount of fat in areas close to the ventricles in which the focus looks fairly old, with formation of

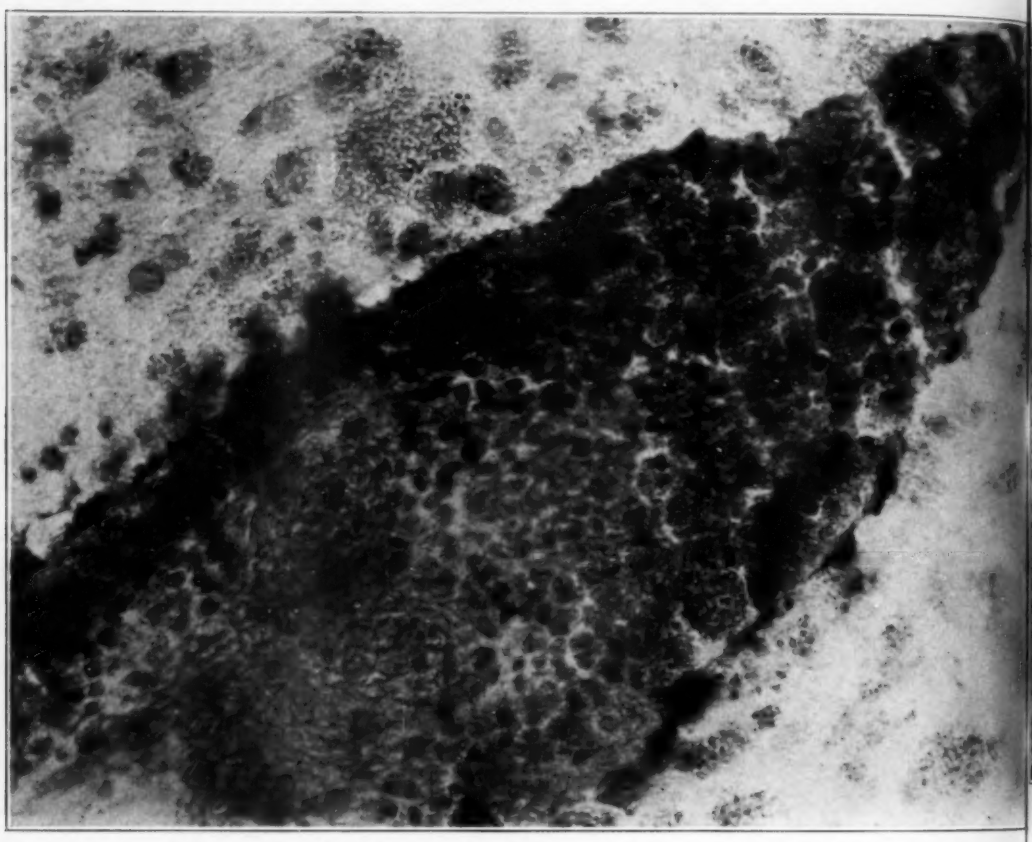

Fig. 15.—Perivascular massing of gitter cells crammed with fat. Scarlet R stain.

fibers and lack of fat-bearing cells. The fat in the ependymal cells is massed in rather large lumps in the basal part of the cell. With a high magnification one can see that the fat is made up of different sized globules, compressed into a large mass which fills and stretches the basal part of the cell like a ball, so that the nucleus, which has retained its normal stainability, is sometimes dislocated toward the free surface of the cell and indented by the mass of fat.

In the area of secondary degeneration (the pyramidal tract), the fat content is very low. In the medulla oblongata immediately above the crossing of the

pyramidal tract there are a few isolated, fat-bearing cells scattered in the periphery of the tract.

Vessels: Changes in the vessels are variously described in the different cases reported. As a rule, the perivascular spaces are greatly dilated in the focal area, less so in the cortex and the more distant, still intact white matter and in the areas of secondary degeneration. In the dilated perivascular spaces there are cell infiltrates of different kinds, either exclusively or predominantly gitter cells, or else gitter cells together with lymphocytes and, less commonly, plasma cells; the last two can also be found to a smaller extent intervascularly; i. e., free in the tissue. It is on the basis of these vascular changes that a great deal of classifica-

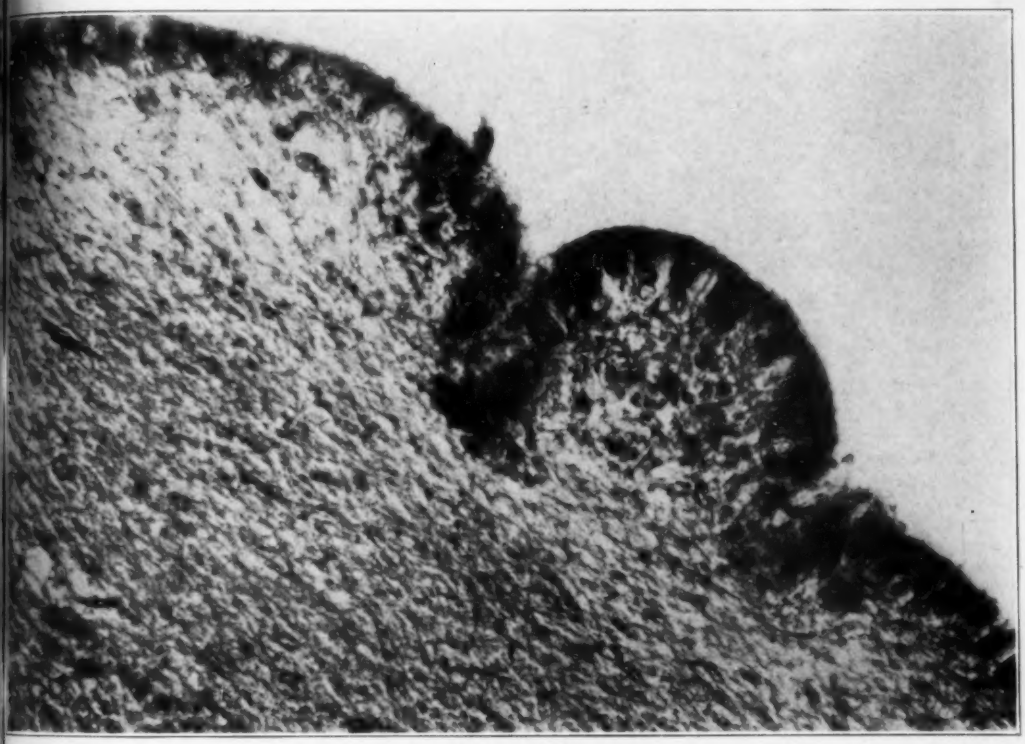

Fig. 16.—Ependyma with fat globules in the basal part. Sudan III stain.

tion has been attempted, but opinions differ considerably as to the definition of the conception of "inflammation." What some authors consider an inflammatory process, others regard as only a degenerative reaction on the same plane as those in other purely degenerative diseases of the central nervous system. The presence of plasma cells has, we believe, usually been regarded as an indication of inflammation. The lymphocyte reaction on which Schilder based his use of the term "encephalitis," on the other hand, has been variously viewed, as such reactions can also be found to a more or less pronounced degree in the periphery of a glioma (Bouman) and in degenerative systemic diseases (Globus and Strauss) as well as in pure encephalitis. The classification will thus be rather vague, and

though it may be possible to refer certain cases to one or the other group, there will always be transitional cases in which the classification is bound to be subjective.

In our case, the character changed in different regions. Dilated perivascular spaces around the vessels were found everywhere in the focal area; they were especially pronounced in the periphery of the areas showing more recent changes, and less pronounced, but still plainly demonstrable, in the areas of older changes and the areas of secondary degeneration as well as in a few places in the lower layers of the cortex. We saw many of the dilated perivascular spaces filled with

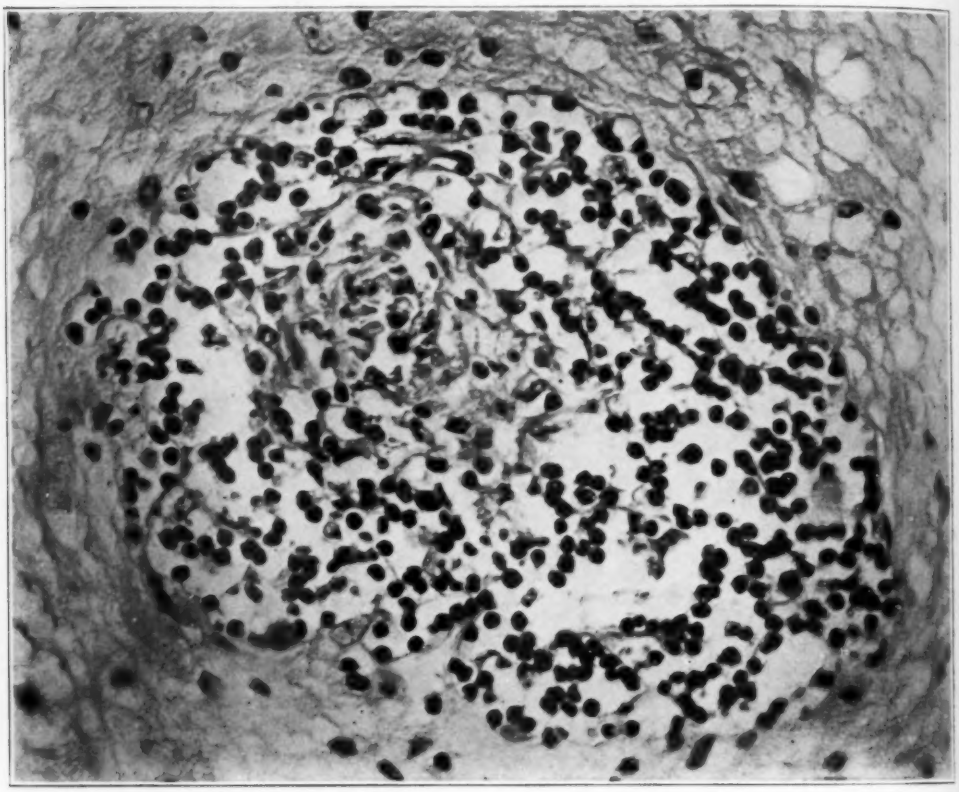

Fig. 17.—Edematous softening of the adventitial spaces with proliferation of connective tissue and massing of lymphocytes. Van Gieson stain.

gitter cells (already described) and here and there an isolated cell of the globoid type. Not all of these cells took the fat stain, and a few took the myelin stain. Sometimes the cells were arranged in as many as four or five layers. Besides these glial elements, we also saw large pale nuclei, by all accounts proliferated endothelium, and fibroblasts which were able to form perfect network structures and even to penetrate the surrounding tissue by means of fibers and nuclei.

In addition to these more degenerative phenomena, we saw transitional forms ranging all the way to dense, black infiltrates of lymphocytes, but only a few cells of the types mentioned. There were plasma cells, but only a few, both in the

perivascular infiltrates and together with lymphocytes in the surrounding tissue, but in many sections they were entirely lacking. We studied carefully the presence of lymphocytes and plasma cells, but were unable to determine whether they ushered in the process or appeared later. We did not study the perivascular glia in greater detail than we have already mentioned. The larger vascular changes followed the outlines of the focal area so closely that we could see its limits from them alone. We were unable to find any definite formation of new vessels or any signs of hemorrhage, but we did find pronounced hyperemia, particularly along the edges of the focal areas.

In the pia-arachnoid membrane we found no demonstrable changes with the exception of hyperemia and edema, a very slight increase of the round cells and a few fat phagocytes.

CLINICAL COMMENT

Anatomic examination showed that this was a case of Schilder's disease, a diagnosis already suggested by the clinical picture. However, the clinical symptoms corresponding to the anatomic picture are heterogeneous, though it is possible from a study of the literature to classify the symptoms, at least for most of the cases, into three groups:

1. Symptoms due to the localization of the disease in various areas of the semioval center, destroying the passages to the different sensory centers in the cortex. Cerebral blindness is often an initial symptom, frequently beginning as hemianopia and progressing to complete blindness. The absence of central scotoma and the patient's retained perception of powerful light, even in the later stages of the disease, indicate, according to Bouman, that the process does not begin at the visual center, and that the axis cylinders are intact. In our case, the blindness appeared at an advanced stage. The initial symptom was, instead, deafness due to disease of the temporal lobe. Cases beginning with deafness have been reported previously, but are not so common (Bullard and Southard; Stewart, Greenfield and Blandy,[24] and others). There was also aphasia.

2. Mental symptoms ranging from disorientation and slight apathy to stupor or profound coma toward the end. Our patient passed through several of these stages to almost complete loss of consciousness. Such symptoms dominate, especially in diseases of the frontal lobes, and are easily explained by the great extent of the process and its diffuse character.

3. If the foci are located in the region under the central convolutions, spastic hemiplegia will develop and, because of the symmetry of the foci, will often become tetraplegia. This was the case in our patient. He also had convulsive attacks in the early stages of the disease, another not uncommon symptom. In general, the symptoms indicated an

24. Stewart; Greenfield, and Blandy: Encephalitis Periaxialis Diffusa: Report of Three Cases with Pathological Examinations, Brain **50**:1, 1927.

extended and diffuse process in the hemispheres. In addition, our case showed symptoms from involvement of the basal ganglia (paramimia, general rigidity, athetosis) and the cerebellum (ataxia).

Cases occur, though rarely, in which there are symptoms not only from the hemispheres, but also from focal areas otherwise located, for instance, the pons, the medulla oblongata or the basal ganglia. In these cases the differential diagnosis of Schilder's disease as opposed to multiple sclerosis, especially its acute form, may be difficult, both clinically and anatomically. Schilder himself emphasized this. In our case, it was to some extent the patient's age, the latent character of the disease with no known antecedents, the considerable extent of the process and the comparatively pronounced inflammatory element in the cerebrospinal fluid that indicated diffuse encephalitis rather than multiple sclerosis. In Schilder's disease the cerebrospinal fluid is more often normal or contains, at the most, a moderate increase of globulin or cells.

There are practically no symptoms from the cranial nerves in Schilder's disease. Headaches, vomiting and papillary stasis, i. e., symptoms of raised intracranial pressure, on the other hand, are common (though they were absent in our case) and simulate those of a tumor in the cerebrum. If one has occasion to observe a case from an early stage, the bilaterality frequently present from the start, the great extent of the symptoms in the hemispheres and the moderate increase in pressure should exclude a diagnosis of tumor.

The course of the disease is usually subacute. It may appear in persons of any age, but is commonest in childhood and youth, developing in a few days and progressing for from a few months to three or four years, though lasting as a rule about one year. In exceptional cases there are remissions; otherwise the disease is always fatal after the periods mentioned. The course of the decidedly chronic form (Foix) has not yet been sufficiently studied, but according to report, there may be a slowly progressing course to death or to a final stage with more or less serious sequelae in the form of paresis or contracture.

Therapeutically, we are helpless. In our case, we tried injections of neoarsphenamine and sulphosin without the slightest effect.

GENERAL COMMENT

From the literature it is difficult to obtain a clear picture of Schilder's disease, its character and its manifestations as a specific disease. One will find many different and frequently diametrically opposed views as to the nature of the disease and its distinction from other diseases of the central nervous system.

Since 1912, many authors have been carefully studying Schilder's disease and reporting new cases. As the material grew, however, the

original definition proved too limited and had to be corrected in several respects. On the other hand, attempts have been made to limit the pathologic picture by the formulation of definite theories as to its specific nature; on the basis of these, certain cases were grouped as typical and others excluded as more or less doubtful or possibly belonging together as a special disease group. The theories thus formulated as to the basic character of the disease fall into three main groups, some authors regarding it as an inflammatory process, others as a degenerative one and still others as a neoplastic one. Austregesilo, Gallotti and Borges suggested a fourth possibility, the "théorie mixte," according to which Schilder's disease has two forms, an inflammatory and a degenerative one.

Of the hypotheses mentioned, the neoplastic theory has gradually lost ground and need hardly be considered. In exceptional cases an actual neoplastic proliferation involving the meninges has been found, but these cases are to be referred to an entirely different pathologic process, viz., glioma.

It is in the nature of the case that a limitation or classification based on phenomena that are themselves not clearly defined must necessarily be arbitrary or at least subjective, easily influenced by the observer's impressions in his own case. This is especially so in the choice between inflammation and degeneration. As we have already pointed out in the description of our case, these conceptions are vague, as the determining factor is as uncertain a symptom as the extent of the reaction of the mesodermal cells. Attempts have therefore been made to define these conceptions more precisely. Schilder did so with regard to inflammation, which is what he considered the disease to be, as he explained in detail. Globus and Strauss, who regarded the condition as degenerative, defined degeneration as "a dissolution of highly specialized tissue," and inflammation as "the constructive, productive responses of mesodermal derivatives." Later, however, they admitted that a fairly pronounced mesodermal reaction may be regarded as part of the complex of degeneration. Bouman called attention to the mesodermal reaction frequently found in the periphery of a glioma. Gouttmann, who accepted the inflammation theory, mentioned as examples of different opinions the fact that Schilder's first case was regarded as inflammatory by Schilder himself, as degenerative by Neubürger and as a tumor by Cassierer and Lewy. There is thus little hope that a classification on these grounds will be generally accepted.

Our case presented a pronounced inflammatory character in some sections and an equally pronounced degenerative one in others, so that its reference to one or the other group would be purely a matter of choice.

In the discussion of these cases, other questions than those mentioned were also considered; among others, that of the familial nature of the

disease. It has been possible to demonstrate the existence of such a familial form, though in only a few cases (Bullard and Southard, Haberfield and Spieler, Krabbe, Ferraro, and Symonds) in which several brothers and sisters of the patient died of "meningitis," "convulsions," "brain fever," etc. Gouttmann believed that such cases constitute a heredofamilial form which, together with the degenerative forms, should be distinguished from Schilder's disease. In this connection, Weimann called attention to the relation between this heredofamilial group and Pelizaeus and Merzbacher's disease and amaurotic family idiocy. However, most authors have no decided opinion as to the familial nature of the disease, which as a matter of fact cannot be regarded as fully proved.

Aside from this, however, further points of contact have been found between Schilder's disease and a number of other diseases, more or less well defined. This has been given due consideration in criticism and classification, and symptoms specifically characteristic of Schilder's disease have been sought. However, they proved difficult to find. Thus, Schilder himself pointed out the resemblance of this disease to Merzbacher's disease, but did not venture to make any definite statement as to their identity. Globus and Strauss could find no actual difference between them; they mentioned the familial character of both diseases. They also discussed Virchow's congenital interstitial encephalitis, and did not think it impossible that several cases reported as this condition really were cases of Schilder's disease. Gagel called attention to the systemic diseases, but also attempted with the aid of the clinical picture to separate a "nuclear group" (as he called a subdivision of diffuse sclerosis) of five cases. Resemblances have also been found to Westphal's pseudosclerosis (Haberfield and Spieler). Flatau [25] somewhat vaguely distinguished Schilder's disease from tuberous sclerosis by the presence of a disease of the optic nerve in the former, but such a condition may be found also in the latter disease and may be absent in the former.

It has been difficult to distinguish Schilder's disease from multiple sclerosis. Whether or not multiple sclerosis appears in childhood has long been regarded as uncertain. Schilder (1912) and Lewy [26] (1924) were doubtful as to whether Schilder's disease might not represent such an infantile form of multiple sclerosis. Later (in 1913), Schilder [27] reviewed the literature and found at least two cases of typical multiple

25. Flatau: Encephaloleucopathia scleroticans progressiva, Encéphale **20**:475, 1925.

26. Lewy: Die diffuse Sklerose (Encephalitis periaxialis diffusa), in Kraus, F., and Brugsch, T.: Spezielle Pathologie und Therapie, Berlin, Urban & Schwarzenberg, 1924, vol. 10, p. 155.

27. Schilder: Zur Frage der Encephalitis periaxialis diffusa (sogenannte diffuse Sklerose), Ztschr. f. d. ges. Neurol. & Psychiat. **15**:359, 1913.

sclerosis in children. In 1922, Wechsler [28] studied critically the different compilations of cases in childhood, and drew the conclusion that the occurrence of multiple sclerosis in children under 15 years of age has been proved, though not absolutely except in a few of the cases reported. This doubt as to the differential diagnosis with regard to multiple sclerosis is natural in view of the striking agreement in histologic detail, a circumstance to which attention is called by many authorities (Lewy, Bouman, Urechia, Mihalescu and Elekes,[29] Schaltenbrand, Stewart, Greenfield and Blandy, Globus and Strauss, and others). Undoubtedly, multiple sclerosis is still a moot question, in spite of all the study given it, but it should not be difficult to distinguish between typical cases of Schilder's disease and of multiple sclerosis because of the great extent of the focal areas in the former disease; this is considered specific by some authors, but there are many cases in which, besides these large main focal areas, a few small, isolated ones will be found scattered in the cerebrum, occasionally also in the cerebellum, pons, medulla oblongata and spinal medulla. There are also cases in which the small size of the foci makes the diagnosis of Schilder's disease doubtful (Urechia, Mihalescu and Elekes, Stewart, Greenfield and Blandy's case 3, and others). In the attempts at differential diagnosis in these doubtful cases, the more or less distinct outlines of the foci have also been suggested, though rather vaguely; occasionally, the presence of symmetrical foci in Schilder's disease has been mentioned, or the fact that in multiple sclerosis, but not in Schilder's disease, the focal areas are produced by the confluence of smaller ones; but these assertions are made with no great degree of conviction. Globus and Strauss chose another method, consistently excluding from the specific disease all changes that are not in full agreement with those making up the pathologic picture in Schilder's original definition. In this connection, they excluded, among others, Schilder's own case 3 (1924). They excluded other cases because of the patient's age, the clinical symptoms (such as remission) and possible deviation from the changes that they regarded as typical in the macroscopic and microscopic appearance. They motivated this rigorous selection by the great value of a strictly limited definition, since all sorts of diseases, particularly multiple sclerosis, might otherwise be included.

In this connection, the disease known as disseminated encephalitis, described by Westphal in 1874, should be mentioned. It is at present no longer distinguished from acute multiple sclerosis (Wimmer, Rönne,

28. Wechsler, I. S.: Statistics of Multiple Sclerosis, Arch. Neurol. & Psychiat. **8**:59 (July) 1922.

29. Urechia; Mihalescu and Elekes: L'encéphalite périaxiale diffuse, type Schilder, Encéphale **19**:617, 1924.

Pette, Marcus and others). In the description given by Henneberg,[30] it strikingly resembles Schilder's disease.

We do not feel justified in determining the type of Schilder's disease after having studied only one case. We are confronted by a disease which only a comparatively short time ago was described as uniform and specific; but hitherto, it has been possible to study it only as a pathologic picture that varied from one case to the next, and presented larger or smaller deviations from the clinical course and the anatomic picture suggested as characteristic. Schilder [31] was cautious in expressing himself in his last published article. He did not venture to make any sharp distinctions; on the contrary, he devoted a great deal of space to proving analogies with other diseases. However, this caution does not appeal to every one, and Globus and Strauss made a serious attempt to set up a definition limiting the conception of the disease, but the limits set up by them appear arbitrary. In their demand for restriction to the original definition given, they excluded cases which deviate from the type only in the age of the patient or in the occurrence of remission.

As for differentiation from other diseases, we must be prepared to recognize that perhaps Schilder's "encephalitis periaxialis diffusa," even in its most typical form, cannot eventually be considered as a specific disease. The decision will be dependent, of course, on the establishment of an etiologic factor, as to which we have hitherto only been able to guess. It has been suggested that Schilder's disease and others related to it may have the same etiology, but that the etiologic factor may have varying modes of attack, thus giving rise to pathologic pictures suggesting different diseases. Naturally, one is unwilling to limit too sharply a subject about which there is still so much debate, but it is also undesirable not to limit it at all merely because such a limitation must often be arbitrary and within doubtful transitional regions, and because by so doing one relinquishes all thoughts of giving the disease its specific place. In a large number of diseases of the central nervous system about the etiology of which there is still much debate it has been possible to find certain symptom-complexes that are regarded as typical for those diseases. We and many other writers consider this a sufficient reason to consider them as separate diseases, at least so long as nosologic research has revealed no new factors. Of course, this applies also to Schilder's disease. The establishment of this disease as an entity has been accepted by many investigators, and in our opinion rightly so, as a point of departure for further study.

30. Henneberg: Handbuch der Neurologie, Berlin, 1911, vol. 3.

31. Schilder: Die Encephalitis periaxialis diffusa, Arch. f. Psychiat. **71**:327, 1924.

If we thus regard Schilder's disease as a specific entity with possibly a specific etiology, we must not forget that it has not been studied long, and that it may reveal different aspects with both clinical and anatomic variations. A classification that aims only at certain details in the symptom-complex and excludes from the disease cases which present deviation from these details risks being incorrect. We shall abstain from a more detailed discussion of the various attempts that have been made at grouping and classifying Schilder's disease, as we feel that little has hitherto been gained by them.

As we mentioned by way of introduction, the only subdivision of the disease that has been generally accepted is the chronic form. Schilder himself included it without further comment, and the undoubted resemblance between it and the other cases of the disease probably justifies this. According to J. Marie, it is essentially a healing stage, and may thus be regarded, to some extent, as an abortive form of the disease, the main difference being that the chronic form is not fatal. A case has also been described in which the symptoms (ataxia, sensory disturbances, spasticity, loss of reflexes, paralysis and defective speech) lasted for thirteen years before the patient died (Kraus and Weil). This must, of course, be regarded as a chronic case, and accordingly forms a sort of transition between the acute or subacute, fatal cases and the chronic, not fatal, cases. It thus appears as though Schilder's disease, the course of which may vary from a few weeks to three or four years without becoming atypical, might also last much longer, so that one obtains a slow progression or even the picture of a cured disease with symptoms of cicatrization.

It is obvious that when there are so many different opinions about the disease there will also be many different names. Schilder himself admitted that his term "encephalitis periaxialis diffusa" does not cover all the possibilities, and this criticism probably also applies in all the other cases in which the names were given with the purpose of describing the essential symptoms. The following are only some of the terms that we have found: "encephalitis periaxialis diffusa" (Schilder), "sclérose (intra-)cérébrale centrolobaire et symétrique" (Marie and Foix), "diffuse Sklerose" (Gagel), "perivasculäre Marknekrose" (Krabbe), "encephaloleucopathia scleroticans" (Flatau), "encephalomyelomalacia chronica diffusa" (Hermel), "progressive degenerative subcortical encephalopathy" (Globus and Strauss), "leucoencéphalopathie diffuse" (Austregesilo, Gallotti and Borges) and "encéphalomyélite diffuse" (Jakob). From a purely practical point of view, this confusion of terms must be disadvantageous. Only one who has given this disease closer study can guess that all these names refer to one and the same pathologic picture.

We have used the term "Schilder's disease" purposely, giving only the name of the discoverer and avoiding all attempts at clinical or anatomic characterization, which have hitherto been unsuccessful. Indeed, it is worth noting that all the terms suggested have, as a rule, been supplied with an explanatory subhead in which Schilder's name has been the accepted mark of uniformity ("Schilder's encephalitis," "maladie de Schilder," etc.).

THE EFFECTS OF LOCAL FREEZING OF THE CENTRAL NERVOUS SYSTEM OF THE CAT*

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In connection with his work on experimental convulsions, Speransky,[1] in 1926, reported a method of producing epileptiform fits in dogs by freezing portions of the cerebral cortex. We here report our observations when this work was repeated.

His method, briefly, was as follows:

A small area of the cortex, excluding the motor area, was frozen through the dura to a depth of from 2 to 4 mm. by means of carbon dioxide gas for about one minute. This procedure was invariably followed in from two to five hours by severe epileptiform convulsions which, in from twelve to fifty hours, resulted in death. Speransky did not state whether an anesthetic was used. He described the convulsions as consisting first of a tonic contraction of the flexors of the hind legs and occasionally clonic convulsions of single muscles or groups of muscles. Following this there were rhythmic tonic and clonic convulsions of large groups of muscles, a latent period of several hours and then marked hyperexcitability, coma and death. However, a point of great interest was that the removal of the frozen area inhibited or aborted the convulsions. On the other hand, the transplantation of portions of the frozen cortex into the subdural space of a healthy animal resulted in similar, though milder, convulsions which ceased spontaneously after a certain lapse of time.

The phenomena described were explained by Speransky on the hypothesis of the formation in the frozen area of an "autoneurotoxin," which is disseminated throughout the central nervous system and body by the spinal fluid and blood. The influence of the spinal fluid was apparently demonstrated by the fact that drainage of the fluid prior to the freezing caused a sharp delay in the reaction time.[2] Furthermore, transfusion of spinal fluid from an animal in which the cortex had been frozen resulted in a similar, but again milder, set of symptoms.

In repeating these interesting experiments, we naturally expected to obtain the same results and in addition to study the morphologic changes produced in the frozen areas. We hope that the latter investigation will prove of interest, as a thorough search through the literature

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1. Speransky, A.: La congelation des tissus, Ann. de l'Inst. Pasteur **40**:213, 1926.

2. Speransky, A.: L'influence du liquide céphalo-rachidien sur l'évolution des procès physiologiques et pathologiques du cerveau, Ann. de l'Inst. Pasteur **40**:755, 1926.

of pathology has uncovered only vague and often unsubstantiated statements as to the changes produced by the direct application of cold to the cerebral cortex.

METHODS

Cats were the animals used. With all sterile precautions and under light ether anesthesia, a trephine hole was made in the temporoparietal region, well behind the motor area, and the meninges were exposed. In some cases the pia was uncovered; in others the dura was left intact. An area about 1.5 cm. square was then frozen to a depth of from 2 to 4 mm. either with an ethyl chloride spray or by the direct application of carbon dioxide snow. These substances were applied for one minute, as in Speransky's experiment. On the removal of the spray or the

Effects of Freezing the Cortex and Lumbar Cord in Animals

Animal	Frozen with	Dura	Postoperative Course	Result
		Cortex		
Dog 1	Ethyl chloride	Intact	Uneventful	Recovery
Cat 1	Ethyl chloride	Reflected	Uneventful	Recovery
Cat 2	Ethyl chloride	Intact	Uneventful	Recovery
Cat 3	Ethyl chloride	Intact	Uneventful	Recovery
Cat 4	Ethyl chloride	Intact	Uneventful	Recovery
Cat 5	Ethyl chloride	Intact	Uneventful	Recovery
Cat 6	Ethyl chloride	Reflected	Intermittent fits 4 hours	Recovery
Cat 7	Carbon dioxide snow	Intact	Uneventful	Recovery
Cat 8	Carbon dioxide snow	Reflected	Uneventful	Recovery
Cat 9	Carbon dioxide snow	Reflected	Uneventful	Recovery
		Cord		
Cat 10	Ethyl chloride	Intact	Flaccid paralysis of hind limbs	Recovery in 1 week
Cat 11	Ethyl chloride	Intact	Flaccid paralysis of hind limbs	Recovery in 4 weeks
Cat 12	Ethyl chloride	Intact	Flaccid paralysis of hind limbs	Recovery in 4 weeks
Cat 13	Carbon dioxide snow	Reflected	Flaccid paralysis of hind limbs	Recovery in 4 weeks
Cat 14	Carbon dioxide snow	Intact	Flaccid paralysis of hind limbs	Recovery in 3 weeks
Cat 15	Carbon dioxide snow	Reflected	Flaccid paralysis of hind limbs	Recovery in 10 days
Cat 16	Carbon dioxide snow	Intact	Flaccid paralysis of hind limbs	Recovery in 3 weeks

snow, the area thawed rather rapidly, returning to normal consistency in about thirty seconds. Muscle and skin were then sutured, and the animal was allowed to recover from the anesthetic. In another series of animals the cord in the lumbar region was similarly frozen. One dog also was used.

OBSERVATIONS

In all, thirty animals were used. In none was there observed anything resembling the picture described by Speransky. In only one was any marked postoperative excitement noted (intermittent, short, generalized clonic fits for four hours); this soon disappeared and the cat recovered perfectly.

The accompanying table summarizes the procedure and results obtained in animals after the cortex or lumbar cord was frozen either with ethyl chloride or with carbon dioxide snow.

The table includes only the animals that were examined histologically at autopsy. The results obtained were uniform; in but one animal of the series (cat 6) did anything approximating an epileptiform convulsion occur, and this may possibly be explained by a slip of the trephine and consequent damage to the cortex. In this animal, after recovery from the anesthetic, fits occurred every fifteen or thirty minutes for four hours. The fits were generalized clonic convulsions lasting about thirty seconds. For about five minutes after each fit the animal was stuporous. None occurred later than four hours after the operation. This animal recovered in four hours and thereafter showed no signs of hyperexcitability. In all other animals with frozen cortices recovery was immediate and complete; they remained normal in every observable detail.

The effects following freezing of the cord with either carbon dioxide snow or ethyl chloride were the same. The animals showed a mild degree of hyperexcitability for from one to three hours after the operation. The hind limbs suffered a complete flaccid paralysis which persisted for some time. However, considering the insult to the cord, recovery was rapid, beginning in from two to three weeks. At first the animal regained ability to support its weight and maintain a standing position. Complete return of function followed soon after. The intactness of the dura seemed to have no effect on the severity of the remittent symptoms. The animals were allowed to live for periods of from one week to three months.

HISTOLOGIC EXAMINATION

The frozen areas of the cortex and cord were removed and control blocks taken from the same animals either from the opposite side, for the cortex, or above the frozen area, for the cord. These blocks were fixed in a diluted solution of neutral formaldehyde, U. S. P. (1:10), dehydrated, embedded in paraffin and stained with hematoxylin and eosin, cresyl violet, iron hematoxylin and phosphotungstic acid hematoxylin.

Changes in the Cortex.—The histologic picture was the same for ethyl chloride and carbon dioxide snow. On the first day after freezing, no changes were seen. One week later, only a slight degree of chromatolysis of a few cells of the lamina granularis externa (layer 2 of Brodmann) and of the lamina pyramidalis (layer 3) could be made out. The glia cells of the marginal layer appeared slightly decreased (fig. 1). At two weeks, the change was more marked (fig. 2), but it was only at the third week that it was definite. At this time, the glia cells of the marginal layer were definitely increased, as were those of the immediately subjacent layers (fig. 3). The glia cells of the marginal layer, more numerous near adhesions, were small, granular and sharply stained and resembled gitter cells (figs. 5 and 6). The glia cells in the submarginal layers were larger, vacuolated, stained less deeply and contained few granules. The pyramidal cells of the second and third layers now appeared in some instances to be undergoing definite neuronophagia. At three months, the appearance was that of a normal cortex, except for a persistent

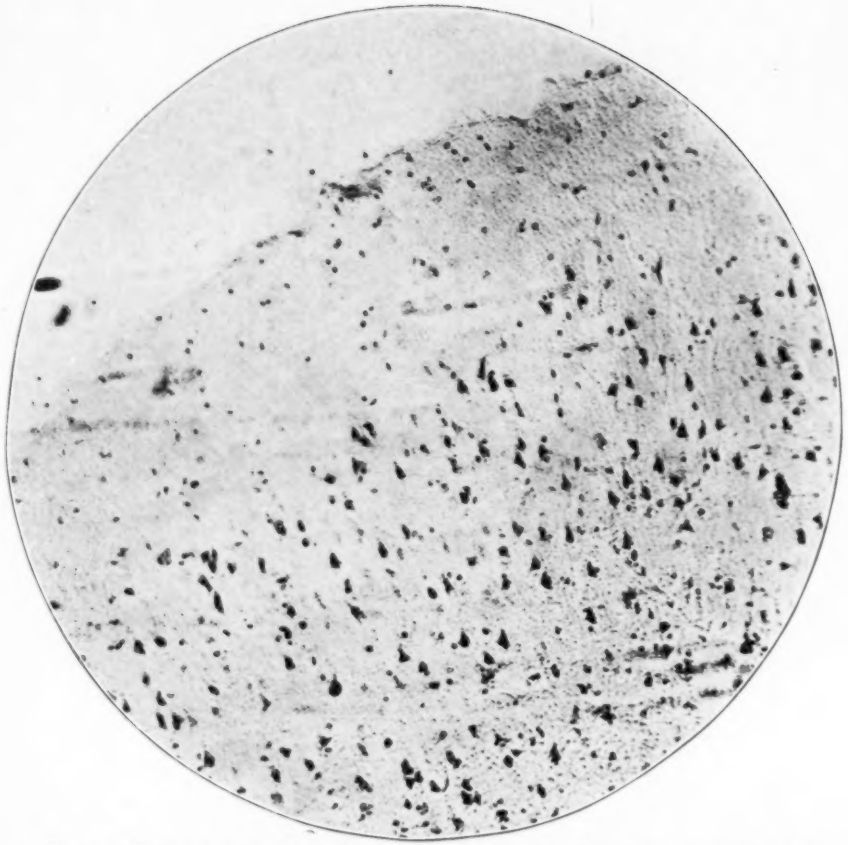

Fig. 1.—Photomicrograph of the cortex at one week, showing a decrease in the marginal glia. Cresyl violet; × 160.

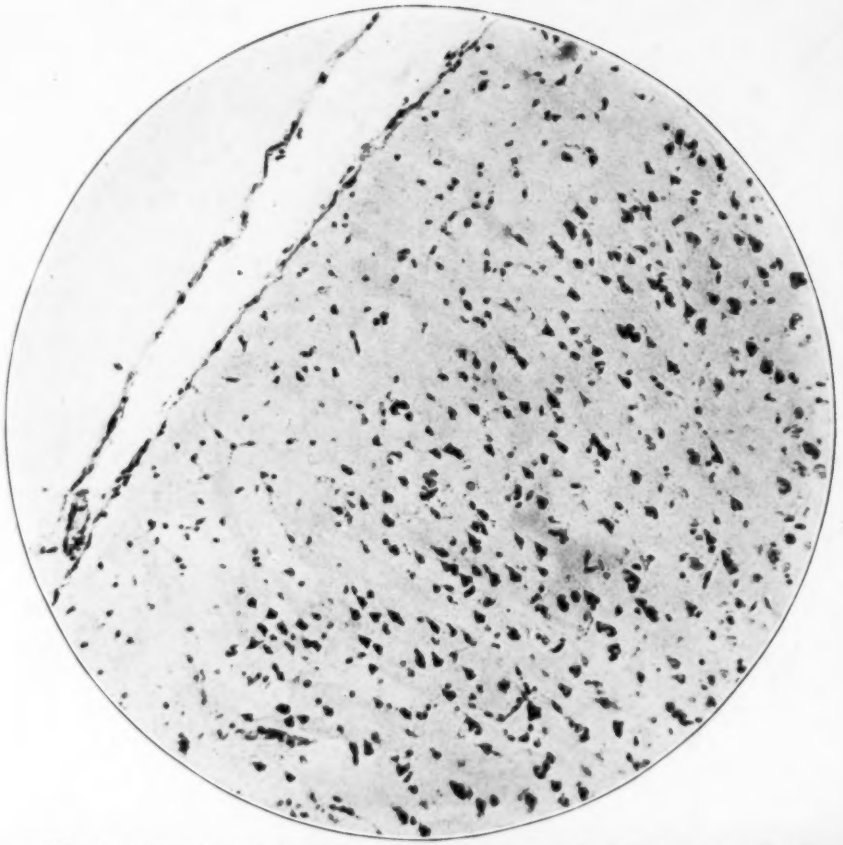

Fig. 2.—Photomicrograph of the cortex at two weeks, showing a beginning increase in the marginal glia. Cresyl violet; × 160.

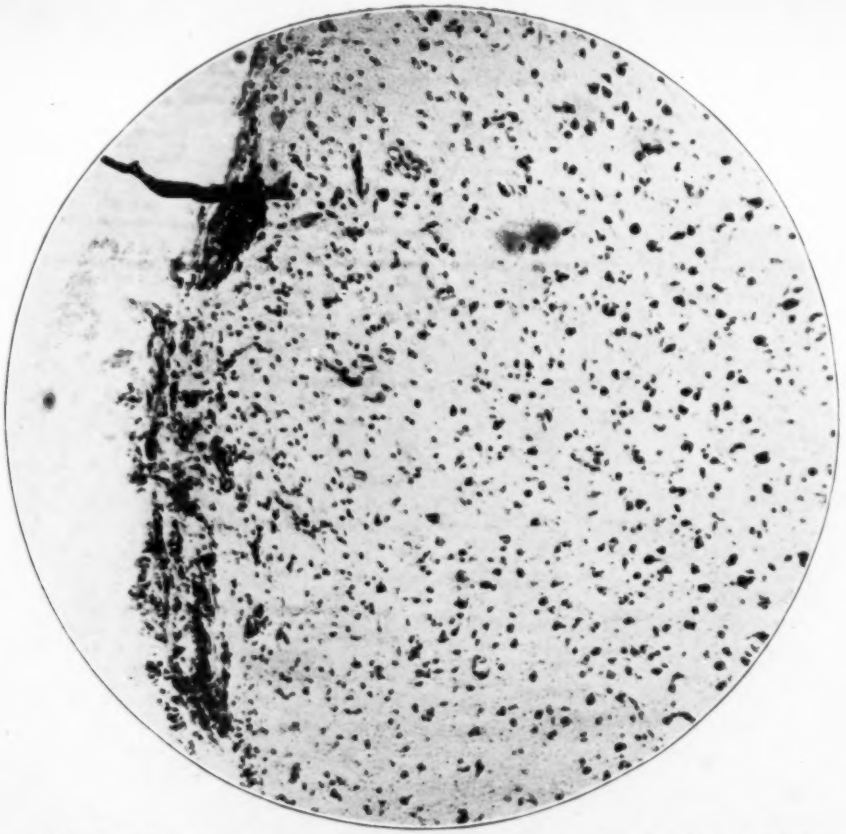

Fig. 3.—Photomicrograph of the cortex at three weeks, showing a definite increase in glia, with distortion of the normal cellular arrangements. Cresyl violet; × 160.

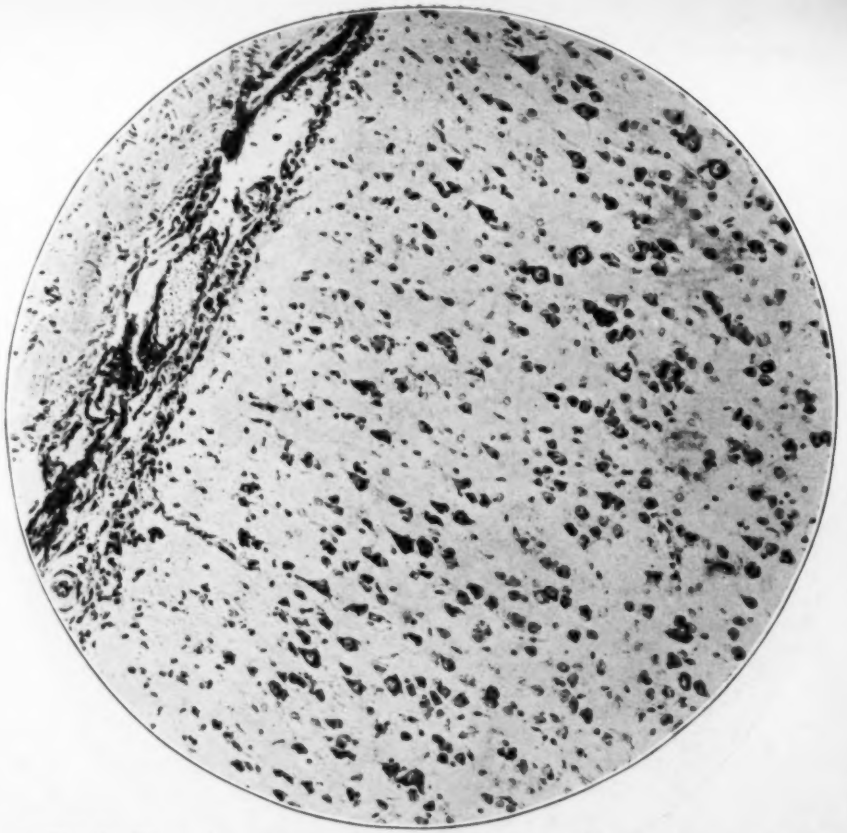

Fig. 4.—Photomicrograph of the cortex at three months, showing a persistent increase in glia in the marginal layer and normal architecture. Cresyl violet; × 160.

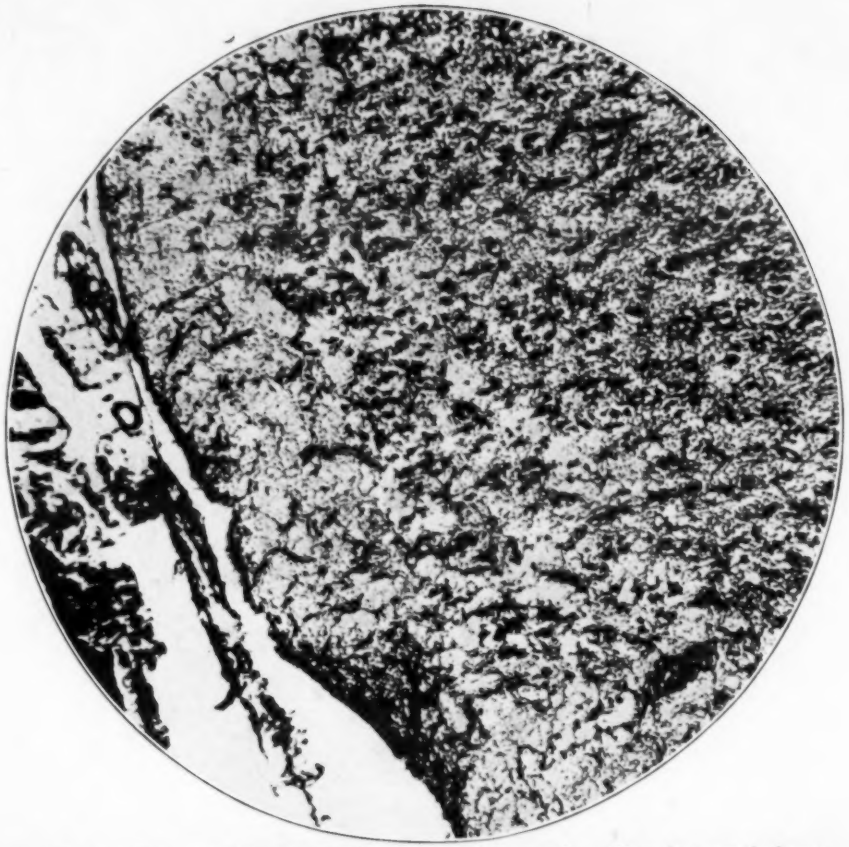

Fig 5.—Photomicrograph of the cortex at three weeks. Phosphotungstic hematoxylin; × 160.

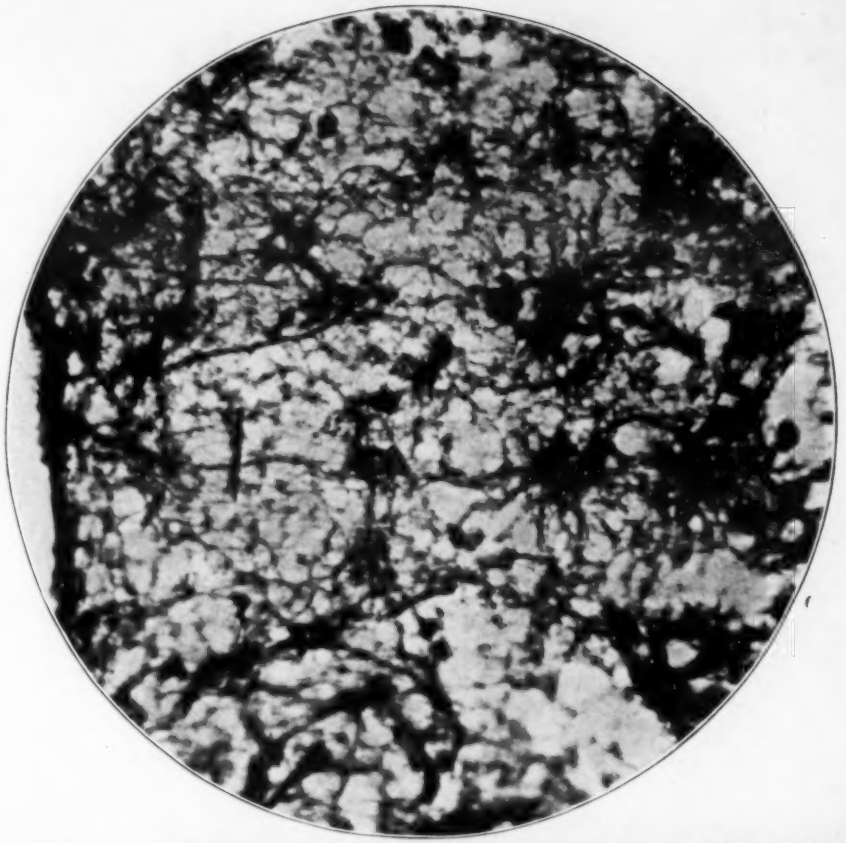

Fig. 6.—Photomicrograph of the cortex at three weeks. Phosphotungstic hematoxylin; × 400.

increase in the number of small marginal glia cells (fig. 4). At this stage all forms of abnormal glia cells had disappeared.

Changes in the Lumbar Cord.—Examination of the frozen areas and of sections taken from above and below them showed no degenerative changes in any of the fiber tracts. It is possible that more exact methods of staining, especially those giving positive pictures, such as osmic acid, would reveal some slight damage. There was a suggestion of an increase in glia in the dorsal half of the cord, though this was by no means as definite as that seen in the cortex. Strangely enough, no changes were discovered in the anterior horn cells, even during the period of paralysis. In the cords in which it was left intact the dura showed a slight thickening but no adhesions. In the operations in which the dura was reflected, adhesions were formed between the torn margins and the pia.

COMMENT

Extensive search through the literature of the past ten years has yielded us practically nothing bearing on the results of the direct application of cold to the central nervous system.

According to a statement of Speransky,[1] we should expect severe, widespread changes throughout the central nervous system, consisting of fatty degeneration of nerve and glia cells, with considerable perivascular infiltration. Bender [3] studied the changes in the brain of a man who died following exposure in freezing weather. He described marked vacuolization of all nerve cells with many small capillary hemorrhages. In small animals (rabbits and guinea-pigs) frozen whole in a salt and brine mixture, miliary hemorrhages were everywhere present in the central nervous system, but no neuronal changes were found. In all animals studied by us the damage was minimal, considering the changes produced in the physical state of the tissue and the presumably marked insult to the nervous system.

SUMMARY

The only clearly recognizable pathologic condition consisted in a moderate degree of glial increase in the marginal and immediately subjacent layers of the cortex, with some evidence of the formation of gitter cells and slight neuronophagia. The dura appears to exert little if any protective influence in these cases. The paralyses produced by freezing of the cord are transitory only, and this, together with the lack of objective changes in the cells of the spinal cord, shows conclusively that little if any lasting damage is done by the freezing.

It may be suggested that possibly the changes observed are due primarily to the temporary anemia and anoxemia produced by the stoppage of circulation during freezing. The changes described and pictured

3. Bender, L.: Lesions in the Brain Caused by Freezing, Arch. Neurol. & Psychiat. **20**:319 (Aug.) 1928.

toxylin; × 160.

by Gildea and Cobb correspond closely to those seen in our animals.[4] It may also be noted that the time after operation at which the neuroglial reaction is at its height (three weeks) corresponds with that described for other types of injuries of the brain.[5]

CONCLUSIONS

Freezing of portions of the cerebral cortex (temporoparietal) in cats does not result in any form of convulsion. Freezing of the spinal cord causes temporary paraplegia.

Morphologic changes in the frozen area are comparatively slight and may possibly be due to temporary anemia.

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4. Gildea, E., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

5. Linell, E.: The Histology of Neuroglial Changes Following Cerebral Trauma, Arch. Neurol. & Psychiat. **22**:926 (Nov.) 1929.

THE EQUILIBRIUM BETWEEN CEREBROSPINAL FLUID AND BLOOD PLASMA

I. THE COMPOSITION OF THE HUMAN CEREBROSPINAL FLUID AND BLOOD PLASMA*

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Mestrezat[1] in his monograph described the cerebrospinal fluid as a dialysate in osmotic equilibrium with the blood plasma. The most important evidence favoring this conception has been reviewed in some detail in several papers by one of us.[2] The quantitative description of the equilibrium between the blood plasma and such a protein-free dialysate as the cerebrospinal fluid is important not only in furthering the understanding of the cerebrospinal fluid itself, but also because the cerebrospinal fluid represents the only protein-free dialysate in the organism present in sufficiently large quantities for adequate analysis.

Mestrezat[1] called attention to the close analogy between the cerebrospinal fluid and the aqueous humor of the eye. He,[3] and independently, two of us (F. F.-S. and M. E. D.[4]) suggested an analogy between the cerebrospinal fluid and the intercellular fluids. One of us (F. F.-S.)[2] also noted that the glomerular filtrate bears a close analogy to the cerebrospinal fluid.

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* From the Department of Neuropathology, Harvard Medical School; the Cerebrospinal Fluid Laboratory, Massachusetts General Hospital; the Neurological Laboratory and the Thorndike Memorial Laboratory, Boston City Hospital.

1. Mestrezat, W.: Le liquide céphalo-rachidien, Paris, A. Maloine et fils, 1912.

2. Fremont-Smith, F.: Nature of Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **17**:317 (March) 1927. Fremont-Smith, F., and Forbes, H. S.: Intra-Ocular and Intracranial Pressure, Arch. Neurol. & Psychiat. **18**:550 (Oct.) 1927. Fremont-Smith, F., and Kubie, L. S.: The Intracranial Pressure in Health and Disease, Baltimore, The Williams & Wilkins Company, 1929, ch. 7.

3. Mestrezat, W.: Rev. neurol. **1**:64, 1927.

4. Fremont-Smith, F., and Dailey, M. E.: J. Pharmacol. & Exper. Therap. **27**:255, 1926.

TABLE 1.—*Fasting Patients with Normal Cerebrospinal Fluid*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride,† Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
1	12/10/29	28	75	0	0000000000	0.577	0.573	86	45	24	13	7.9	17	345	425	....	...	317	331	....	....	9.48	0.95	Pulmonary tuberculosis
2	11/17/27	13	195	1	0000000000	0.549	0.548	86	55	21	12	7.5	34	372	439	....	...	...	...	....	....	....	....	Epilepsy
3	12/ 3/28	46	160	2	1222100000	0.580	0.577	108	93	23	20	7.6	24	353	439	4.18	1.3	324	334	9.55	4.85	9.09	0.97	Multiple sclerosis
4	1/24/29	47	190	5	2211000000	0.568	0.567	96	75	42	28	6.3	22	372	447	3.45	1.5	316	324	8.86	4.14	8.99	0.85	Multiple sclerosis
5	11/12/27	50	170	0	.....	0.559	0.559	89	74	29	21	7.6	41	351	439	....	...	...	...	....	....	9.22	....	Undiagnosed
6	12/21/28	42	110	3	1111111100	0.556	0.558	105	64	24	19	7.0	26	348	428	3.81	1.3	303	306	9.7	5.3	9.37	0.97	Pulmonary tuberculosis
7	1/ 4/29	56	80	2	1111000000	0.570	0.568	121	65	30	16	6.6	26	362	439	....	...	314	321	10.0	5.38	8.66	0.94	Undiagnosed
8	4/12/29	32	160	1	0122210000	0.580	0.578	102	64	25	19	7.4	42	351	436	....	...	322	324	....	....	9.32	1.25	Epilepsy
9	3/ 5/29	?	...	3	1121110000	0.588	0.586	90	60	26	19	6.2	26	359	441	....	...	311	324	9.6	4.7	9.1	1.18	Undiagnosed
10*	10/20/28	53	40	1	0111111000	0.582	0.581	111	65	28	19	6.6	29	375	452	....	...	335	343	9.6	4.4	7.93	....	Undiagnosed
11	10/31/27	30	150	4	.....	0.566	0.565	97	70	22	14	7.5	40	362	438	....	...	...	...	....	....	8.95	....	Chronic epidemic encephalitis
12	3/ 1/29	32	170	5	1111100000	0.576	0.578	89	78	30	21	6.2	43	359	439	....	...	315	328	....	....	8.49	1.70	Syphilis of central nervous system
13	12/13/25	14	150	1	0000000000	.....	.....	105	67	37	..	7.3	15	362	441	....	...	...	...	....	....	....	....	Undiagnosed
14	5/15/25	46	130	4	0000000000	.....	.....	113	69	26	19	7.4	22	364	449	....	...	...	...	....	....	....	....	Hiccups
15	7/ 7/26	52	120	4	0000000000	.....	.....	100	62	31	18	7.9	29	371	451	....	...	...	...	....	....	....	....	Late carbon monoxide poisoning
16	5/26/26	43	130	2	0000000000	.....	.....	78	54	21	14	7.6	28	367	441	....	...	...	...	9.5	4.37	....	....	Myxedema
17	2/27/25	16	200	2	0000000000	.....	.....	112	73	25	..	7.6	25	361	436	....	...	...	...	....	....	....	....	Epilepsy
18	7/15/25	34	135	0	0000111000	.....	.....	88	50	22	21	7.4	25	348	422	....	...	...	...	....	....	....	....	Splenomegaly
19	11/ 5/25	?	100	1	0011000000	.....	.....	103	73	17	14	7.7	34	368	451	....	...	...	...	....	....	....	....	Undiagnosed
20	3/ 4/25	44	140	1	0000000000	.....	.....	92	57	34	22	6.6	20	349	441	....	...	...	...	....	....	....	....	Undiagnosed
21	11/ 4/25	29	170	2	0000000000	.....	.....	91	65	23	20	6.7	24	357	443	....	...	...	...	....	....	....	....	Diabetes insipidus
22	2/ 9/26	42	120	3	0112211000	.....	.....	88	60	29	20	7.3	38	361	444	....	...	...	...	....	....	....	....	Multiple sclerosis
Maximum						0.588	0.586	121	93	42	28	8.0	43	375	452	4.18	1.5	325	343	10.0	5.38	9.48	1.70	
Minimum						0.549	0.548	78	45	17	12	6.2	15	345	422	3.45	1.3	303	306	8.86	4.14	7.93	0.85	
Average						0.571	0.570	98	65	27	18	7.2	29	359	440	3.81	1.4	317	326	9.54	4.73	8.96	1.10	

* Fluid from the cisterna magna.

† Chloride values may be expressed as NaCl by multiplying by the factor 1.65.

TABLE 2.—*Fasting Patients with Normal Cerebrospinal Fluid and Increased Intracranial Pressure*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
23	1/26/28	42	...	1	.....	0.549	0.551	79	65	29	17	7.3	34	361	439	....	...	...	...	....	....	9.1	....	Chronic epidemic encephalitis
24	1/25/28	33	205	0	0000000000	0.557	0.550	84	63	26	16	7.0	25	374	443	....	...	...	...	....	....	8.42	....	Undiagnosed
25	12/12/27	49	230	2	.....	0.589	0.589	109	67	39	27	6.7	34	367	442	....	...	...	...	....	....	8.59	....	Undiagnosed
26	1/14/28	36	...	..	.....	0.550	0.549	85	62	30	17	6.6	26	367	441	....	...	...	...	....	....	7.83	....	Chronic epidemic encephalitis
27	2/ 7/28	36	205	1	.....	0.560	0.555	86	56	26	15	6.8	25	368	442	....	...	...	...	....	....	8.34	....	Chronic epidemic encephalitis
28	2/15/28	42	205	..	.....	0.542	0.541	85	56	27	17	6.8	30	374	439	....	...	...	...	....	....	8.24	....	Chronic epidemic encephalitis
29	1/10/28	19	250	0	.....	0.557	.....	83	64	30	16	7.4	31	361	442	....	...	...	...	....	....	8.83	....	Epilepsy
30	3/ 6/26	16	320	0	0011111100	.....	.....	105	61	26	22	7.5	36	348	437	....	...	...	...	....	....	....	....	Cerebellar glioma
31	2/ 1/26	50	220	2	0000000000	.....	.....	101	72	23	..	7.2	12	356	440	....	...	...	...	....	....	....	....	Undiagnosed
32	3/15/26	16	300	0	0000000000	.....	.....	125	69	23	13	7.3	12	355	442	....	...	...	...	....	....	....	....	Cerebellar tumor
33	12/29/25	26	240	2	0000000000	.....	.....	101	75	30	19	6.9	21	361	443	....	...	...	...	....	....	....	....	Undiagnosed
34	7/20/26	63	250	4	1212000000	.....	.....	94	55	38	26	7.3	33	365	445	....	...	...	...	....	....	....	....	Undiagnosed
35	2/ 9/25	30	430	1	0001100000	.....	.....	82	58	40	19	7.1	24	358	439	....	...	...	...	....	....	....	....	Cerebellar glioma
36*	2/ 9/25	30	400	0	0000000000	.....	.....	82	64	..	..	7.1	5	358	438	....	...	...	...	....	....	....	....	Cerebellar glioma
37*	1/ 2/26	32	270	1	0000000000	.....	.....	119	81	23	18	8.08	8	373	451	....	...	...	...	....	....	....	....	Cerebellar tumor
Maximum						0.589	0.589	125	81	40	27	8.08	34	374	451	....	...	...	...	....	....	9.1		
Minimum						0.542.	0.541	82	55	23	13	6.6	5	348	437	....	...	...	...	....	....	7.83		
Average						0.558	0.557	95	64	29	19	7.1	24	360	442	....	...	...	...	....	....	8.42		

* Fluid from the lateral ventricle.

TABLE 3.—*Minor Abnormalities in the Cerebrospinal Fluid of Fasting Patients*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
38	11/ 2/28	53	180	3	1110000000	0.565	0.567	97	72	25	16	6.6	25	371	438	....	...	317	326	9.0	4.1	8.33	0.98	Undiagnosed
39	10/20/28	53	80	1	1111100000	0.582	0.584	111	63	28	19	6.6	57	375	450	....	...	335	342	9.6	4.87	7.93	....	Undiagnosed
40	12/15/27	25	130	9	.....	0.567	0.563	92	67	23	14	7.3	29	353	435	....	...	...	...	....	....	8.93	....	Neurasthenia
41	12/11/28	46	140	9	1233210000	0.575	0.573	95	61	33	21	6.5	28	351	435	4.47	...	309	323	9.64	4.84	8.59	0.92	Multiple sclerosis
42	4/27/29	46	...	2	5554321100	0.571	0.573	108	73	24	21	6.4	29	362	438	....	...	315	319	9.8	5.0	8.6	1.21	Multiple sclerosis
43	5/13/29	30	...	1	0000000000	0.560	0.563	94	67	26	18	6.8	55	358	436	....	...	308	324	....	....	8.87	1.15	Undiagnosed
44	10/24/29	24	...	0	0000000000	0.563	0.561	83	52	30	23	6.6	63	370	444	....	...	307	313	....	....	8.1	1.14	Epilepsy
45	1/13/28	66	240	..	.....	0.577	0.560	90	50	32	21	6.9	51	363	431	....	...	...	...	....	....	8.55	....	Dementia paralytica
46	2/ 1/29	72	...	4	0011000000	0.583	0.561	74	57	19	17	6.3	42	373	449	....	...	334	346	....	....	8.38	0.99	Alcoholic neuritis
47	4/25/29	58	...	1	4443211100	0.599	0.576	91	67	33	28	6.7	32	369	449	....	...	305	297	....	....	8.65	1.15	Multiple sclerosis
48	3/26/29	?	...	0	1122210000	0.538	0.559	108	70	27	20	6.9	28	364	439	....	...	314	327	9.48	5.05	8.63	1.08	Chronic nephritis
49	1/25/29	50	...	16	1122200000	0.600	0.575	98	59	30	26	6.1	37	354	444	3.64	1.6	320	304	9.18	4.6	8.04	0.99	Tabes
50	2/26/29	34	65	..	1111000000	0.572	0.584	99	61	24	19	6.2	23	356	444	3.9	2.0	314	315	8.6	4.6	9.02	1.16	Pulmonary tuberculosis
51	4/13/29	58	200	3	0011100000	0.593	0.576	111	68	30	20	6.9	21	358	439	....	...	314	324	9.4	4.8	8.92	0.97	Blue sclerotics, fragilitas ossium
52	1/ 6/28	33	250	0	0001100000	0.588	0.563	114	59	35	26	6.9	17	369	433	....	...	...	...	9.73	....	....	....	Epilepsy
53	3/27/29	30	...	2	1223220000	0.590	0.567	105	69	27	15	6.9	33	375	442	3.9	1.2	322	331	9.74	4.92	8.74	1.10	Multiple sclerosis
54	4/10/29	30	190	3	0123221100	0.582	0.563	92	65	25	..	7.0	35	372	447	....	...	321	329	....	....	9.02	0.91	Multiple sclerosis
55	10/25/28	47	130	1	1112110000	0.582	0.568	108	68	29	15	7.4	63	365	444	....	...	335	348	9.8	4.8	9.34	....	Friedreich's ataxia
56	12/ 5/27	49	250	..	.....	0.583	0.575	117	67	30	16	6.9	24	356	445	....	...	...	...	....	....	8.25	....	Chronic nephritis
57	2/ 8/28	42	...	..	.....	0.543	0.550	95	77	25	17	7.4	37	373	438	....	...	...	...	....	....	8.7	....	Chronic epidemic encephalitis
326	4/22/29	39	90	10	0111000000	0.577	0.574	94	68	20	13	6.7	29	348	431	....	...	311	313	10.0	5.4	8.74	1.17	Diabetes insipidus
58	2/ 6/29	52	130	3	1112221000	0.576	0.585	89	68	19	12	6.8	49	354	441	4.7	1.8	305	316	9.3	4.83	9.26	1.08	Undiagnosed
59	2/ 8/29	42	170	3	1111100000	0.589	0.567	100	64	18	13	6.1	69	362	438	3.0	1.29	342	348	9.3	4.63	8.11	1.09	Amyotrophic lateral sclerosis
60	11/16/27	32	150	5	.....	0.554	.....	106	73	27	14	7.9	33	366	440	....	...	...	...	....	....	8.91	....	Epidemic encephalitis
61	11/ 5/25	33	150	3	0000000000	.....	.....	98	58	18	12	7.2	52	366	445	....	...	...	...	....	....	....	....	Epilepsy
62	3/ 5/25	50	120	0	0022211000	.....	.....	122	73	34	25	8.0	23	347	448	....	...	...	...	....	....	....	....	Undiagnosed
63	6/29/25	53	140	1	0000100000	.....	.....	106	61	22	14	6.5	46	362	447	....	...	...	...	....	....	....	....	Undiagnosed
64	3/13/25	55	180	14	0012211000	.....	.....	98	66	27	21	6.4	58	349	448	....	...	...	...	....	....	....	....	Undiagnosed
65	7/10/25	11	110	16	0001121000	.....	.....	91	60	28	19	6.7	51	351	424	....	...	...	...	....	....	....	....	Anterior poliomyelitis
66	4/ 9/25	17	120	30	0001110000	.....	.....	102	73	32	27	7.8	43	353	437	....	...	...	...	....	....	....	....	Acute epidemic encephalitis
67	12/19/24	24	140	34	1132210000	.....	.....	97	73	26	22	7.0	38	364	453	....	...	...	...	....	....	....	....	Acute epidemic encephalitis
68	3/ 3/25	31	...	1	0012222110	.....	.....	122	75	16	..	7.0	62	353	444	....	...	...	...	....	....	....	....	Tumor of the fourth ventricle
69*	3/ 3/25	31	...	5	2131000000	.....	.....	122	61	16	..	7.0	11	353	435	....	...	...	...	....	....	....	....	Tumor of the fourth ventricle
70	10/24/25	56	230	1	0000111000	.....	.....	102	65	28	16	6.9	66	347	431	....	...	...	...	....	....	....	....	Undiagnosed
71	5/19/25	53	130	10	0001221100	.....	.....	103	60	35	20	6.2	62	351	436	....	...	...	...	....	....	....	....	Undiagnosed
72	6/ 4/26	52	130	1	0000000000	.....	.....	89	68	29	22	8.2	47	350	437	....	...	...	...	....	....	....	....	Myxedema
172	10/29/25	55	95	6	0000110000	.....	.....	99	70	26	20	7.3	56	345	418	....	...	...	...	....	....	....	....	Undiagnosed
73	11/ 5/29	24	145	0	0011110000	0.590	0.590	86	62	27	22	6.6	78	378	447	....	...	316	318	....	....	8.01	1.31	Epilepsy
74	4/18/29	30	155	5	0011100000	0.583	0.575	96	72	20	13	6.7	82	364	433	....	...	321	325	....	....	8.49	1.06	Multiple sclerosis
75	5/10/29	35	...	1	0122100000	0.567	0.580	111	71	26	19	6.7	85	356	436	....	...	323	326	....	....	8.45	0.97	Multiple sclerosis
76	2/14/28	40	110	0	1122210000	0.538	0.540	88	52	23	14	6.8	98	354	433	....	...	...	...	....	....	8.08	....	Multiple sclerosis
77	12/ 1/27	41	80	26	5555555554	0.598	0.603	99	56	26	14	7.5	106	365	438	....	...	...	...	....	....	8.87	....	Dementia paralytica
78	1/31/29	30	...	5	0111110000	0.579	0.579	105	76	15	14	6.4	132	351	431	4.0	1.3	315	324	9.7	4.86	9.21	0.99	Multiple sclerosis
Maximum						0.600	0.603	122	77	35	28	8.2	132	378	453	4.7	2.0	342	348	10.0	5.4	9.34	1.31	
Minimum						0.538	0.540	74	50	15	12	6.1	11	347	424	3.0	1.2	305	297	8.6	4.1	7.93	0.91	
Average						0.575	0.571	100	66	26	19	6.9	49	360	440	3.9	1.5	319	324	9.5	4.8	8.62	1.07	

* Fluid from lateral ventricle.

During the past five years we have made parallel determinations on cerebrospinal fluid and venous blood, obtained at the time of lumbar puncture, in 240 instances on 201 patients, ranging in age from 5 to 75 years. The cases dated from 1924 to September, 1927, inclusive, were studied in the cerebrospinal fluid laboratory at the Massachusetts General Hospital; those after September, 1927, were studied in the neurological laboratory at the Boston City Hospital. In 122 instances the patients had been fasting for nine hours or more before determinations were made (in the vast majority of these the fasting period was twelve hours or more).

TABLE 4.—*Summary of Tables 1, 2 and 3*

	Blood Serum				Cerebrospinal Fluid			
	Maximum	Minimum	Average	No. of Cases	Maximum	Minimum	Average	No. of Cases
Freezing point depression, C.	—0.600	—0.538	—0.571	49	—0.603	—0.540	—0.569	47
Sugar, mg. per 100 cc.	125	74	98	80	93	45	65	80
Nonprotein nitrogen, mg. per 100 cc.	42	15	27	70	28	12	19	73
Protein, Gm. per 100 cc.	8.2	6.1	7.0	80	43*	12*	28*	35*
Chloride, mg. per 100 cc.	378	345	360	80	453	422	440	80
Chloride, as NaCl, mg. per 100 cc.	623	569	594	80	748	697	726	80
Phosphorus, mg. per 100 cc.	4.7	3.0	3.9	10	2.0	1.2	1.5	9
Sodium, mg. per 100 cc.	342	303	318	31	348	297	325	31
Calcium, mg. per 100 cc.	10.0	8.6	9.5	21	5.9	4.1	4.8	20
Total solids, Gm. per 100 Gm.	9.48	7.93	8.71	40	1.70	0.85	1.08	28

* Spinal fluid protein values (expressed as mg. per hundred cubic centimeters) are taken from tables 1 and 2. Values for ventricular fluids are not included. Normal ventricular fluid contains from 5 to 15 mg. protein per hundred cubic centimeters.

The following determinations were made on both cerebrospinal fluid and blood plasma or serum: freezing point depression in 63 instances, sugar in 219 instances, nonprotein nitrogen in 171 instances, sodium in 56 instances, calcium in 39 instances, phosphorus in 13 instances, total solids in 41 instances, protein in 186 instances and chloride in 240 instances. In addition, the cerebrospinal fluid pressure, cell count and colloidal gold and Wassermann reactions have been determined in nearly every case.

METHODS

The freezing point was determined by the method of Beckmann,[5] a Heidenhain thermometer being used; sugar by the method of Folin and Wu,[6] with the modified

5. Findlay, A.: Practical Physical Chemistry, New York, Longmans, Green & Company, 1923, p. 112.

6. Folin, O., and Wu, H.: J. Biol. Chem. **41**:367, 1920.

sugar tubes described by Rothberg and Evans,[7] and nonprotein nitrogen by the method of Folin and Wu.[8] For both these determinations the protein-free filtrate for cerebrospinal fluid and serum or plasma was made with 5 per cent sodium tungstate and third-normal sulphuric acid. Sodium was determined by the Rourke modification[9] of the Kramer-Gittleman method; calcium by the method of Fiske and Logan,[10] phosphorus by the method of Fiske and Subbarow,[11] total solids by drying to a constant weight at from 105 to 110 C., protein in plasma or serum by the Kjeldahl method,[12] from 1 to 5 cc. samples being used; protein in the cerebrospinal fluid by the method of Denis and Ayer;[13] chlorides by the method of Van Slyke,[14] until October, 1928, and subsequently by the modification of Wilson and Ball.[15] Blood was obtained by venous puncture in the antecubital space, special care being taken that there should be only momentary stasis. Until September, 1927, blood was drawn into a dry syringe in which there was just sufficient powdered potassium oxalate to prevent clotting. Immediately after the blood was mixed with the oxalate, it was placed under paraffin oil without exposure to air, immediately centrifugated and the plasma separated. Subsequent to September, 1927, the blood was drawn directly into oil in 50 cc. centrifuge tubes without an anticoagulant. It was centrifugated immediately, the serum was removed, and it was otherwise handled as described for plasma. Protein-free filtrates for sugar determinations were made at once. All determinations were started on the day of the experiment.

Cerebrospinal fluid was obtained at lumbar puncture (occasionally at ventricle or cistern puncture) with the subject in the recumbent position, procaine anesthesia being employed. Spinal fluid pressure was determined by allowing the spinal fluid to rise in a glass manometer having a bore of less than 2 mm. attached directly to the lumbar puncture needle. Special care was taken that the patient should be relaxed at the time that the pressure was read. The spinal fluid was drawn into chemically clean, sterile tubes and immediately capped with rubber stoppers. Protein-free filtrate for sugar was made immediately. Spinal fluid cells were counted in the ordinary blood counting chamber, the cells being faintly stained with Unna's polychrome methylene blue (methylthionine chloride, U.S.P.). The colloidal gold reaction was obtained by the method of Lange as described by Cockrill.[16]

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13. Denis, W., and Ayer, J. B.: Method for Quantitative Determination of Protein in Cerebrospinal Fluid, Arch. Int. Med. **26**:436 (Oct.) 1920. Fremont-Smith, F., and Ayer, J. B.: Human Cerebrospinal Fluid, New York, Paul Hoeber, 1926, ch. 7.

14. Van Slyke, D. D.: J. Biol. Chem. **58**:523, 1923-1924.

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16. Cockrill, J. R.: Comparison of Gold Chlorid, Benzoin and Mastic Tests on Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **14**:455 (Oct.) 1925.

TABLE 5.—*Normal Cerebrospinal Fluid in Patients Not Fasting*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
79	12/ 2/27	16	80	0	0000000000	0.568	0.571	94	72	24	11	7.5	15	370	444	....	...	...	...	....	....	8.84	0.97	Epilepsy
80	7/14/25	40	200	0	0111000000	.....	.....	109	72	20	19	7.3	27	347	430	....	...	...	...	....	....	....	....	Undiagnosed
81	10/16/25	26	180	0	0000000000	.....	.....	95	65	24	22	7.0	33	370	445	....	...	...	...	....	....	....	....	Undiagnosed
82	5/26/25	58	120	4	0000000000	.....	.....	92	61	33	21	7.0	26	350	442	....	...	...	...	....	....	....	....	Chronic epidemic encephalitis
83	4/ 9/25	13	120	2	0011100000	.....	.....	101	68	37	23	7.0	38	361	448	....	...	...	...	....	....	....	....	Sydenham's chorea
84	7/ 1/25	42	90	3	0000000000	.....	.....	104	76	27	23	6.5	27	373	452	....	...	...	...	....	....	....	....	Undiagnosed
85	4/15/25	21	160	2	0000000000	.....	.....	115	69	21	16	6.3	34	365	445	....	...	...	...	....	....	....	....	Undiagnosed
86	7/13/25	34	150	5	0001100000	.....	.....	106	64	26	21	7.0	34	355	433	....	...	...	...	....	....	....	....	Undiagnosed
87	4/21/25	37	180	2	0000111100	.....	.....	123	81	21	17	7.2	41	352	449	....	...	...	...	....	....	....	....	Undiagnosed
88	6/ 2/26	24	160	0	0001210000	.....	.....	105	86	35	19	8.0	35	351	438	....	...	...	...	....	....	....	....	Undiagnosed
89	3/11/25	70	200	..	0001210000	.....	.....	130	87	28	19	6.5	28	367	450	....	...	...	...	....	....	....	....	Peripheral neuritis
90	2/11/25	44	130	2	0000000000	.....	.....	152	86	30	..	6.4	37	362	443	....	...	...	...	....	....	....	....	Progressive muscular atrophy
91*	12/ 2/26	33	130	4	1100000000	.....	.....	130	86	29	13	7.8	19	364	440	....	...	...	...	....	....	....	....	Tumor of the spinal cord
92	5/25/25	13	630	3	0001100000	.....	.....	131	56	45	38	8.2	13	367	452	....	...	...	...	....	....	....	....	Undiagnosed
93	6/26/25	22	270	5	0000000000	.....	.....	98	67	22	17	8.3	23	350	448	....	...	...	...	....	....	....	....	Undiagnosed
94	3/ 4/26	30	160	4	0011100000	.....	.....	97	69	26	18	8.4	41	355	429	....	...	...	...	....	....	....	....	Undiagnosed
95	2/20/26	24	90	3	0011000000	.....	.....	118	58	28	16	6.9	37	351	437	....	...	...	...	....	....	....	....	Acute pharyngitis
163	4/ 1/26	39	140	0	0000000000	.....	.....	90	66	18	15	6.3	22	345	436	....	...	...	...	....	....	....	....	Undiagnosed
Maximum								152	87	45	38	8.4	41	373	452									
Minimum								90	56	18	11	6.3	13	345	429									
Average								111	72	28	21	7.2	30	358	443									

* Fluid from the cisterna magna.

TABLE 6.—*Minor Abnormalities in the Cerebrospinal Fluid of Patients Not Fasting*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
96	4/ 1/29	15	250	7	0000000000	0.557	0.558	124	62	34	22	7.4	24	348	418	5.32	...	302	301	10.14	5.3	8.76	0.93	Embolus to brain
97	6/ 4/25	38	110	7	0000000000	.....	.....	109	74	31	18	7.7	38	355	449	....	...	...	...	....	....	....	....	Undiagnosed
327	2/26/30	51	270	2	1112321000	.....	.....	94	55	34	22	6.8	33	367	441	....	...	311	331	....	....	8.47	1.04	Undiagnosed
98	11/ 9/28	38	...	..	.....	0.547	.....	...	..	18	..	6.7	..	354	431	....	...	311	316	8.53	....	....	....	Undiagnosed
99	4/30/26	33	155	3	1223332110	.....	.....	...	..	25	..	7.3	48	364	441	....	...	...	...	....	....	....	....	Epilepsy
100	2/28/25	33	205	44	0012322110	.....	.....	104	60	32	18	7.4	71	353	436	....	...	...	...	....	....	....	....	Acute myelitis
101*	2/28/25	33	...	25	0012211000	.....	.....	104	61	32	18	7.4	53	353	437	....	...	...	...	....	....	....	....	Acute myelitis
102	7/ 6/25	37	180	40	0012210000	.....	.....	88	72	28	21	6.9	56	362	439	....	...	...	...	....	....	....	....	Undiagnosed
103	3/16/26	49	60	10	0011100000	.....	.....	107	65	25	18	7.8	27	353	432	....	...	...	...	....	....	....	....	Undiagnosed
104	3/15/26	40	80	2	0000000000	.....	.....	109	61	23	17	7.5	48	371	445	....	...	...	...	....	....	....	....	Trigeminal neuralgia
105	3/31/25	40	370	23	0000000000	.....	.....	159	105	20	12	6.6	28	347	428	....	...	...	...	....	....	....	....	Acute carbon monoxide poisoning
106	2/11/25	44	100	14	5555321100	.....	.....	109	78	27	..	7.1	32	370	441	....	...	...	...	....	....	....	....	Multple sclerosis
107	6/30/25	38	140	71	1222211000	.....	.....	98	52	21	18	6.6	40	362	449	....	...	...	...	....	....	....	....	Syphilis of central nervous system
108	9/23/25	48	120	2	0001232100	.....	.....	98	61	22	16	7.6	22	349	433	....	...	...	...	....	....	....	....	Undiagnosed
109	7/ 1/25	30	120	5	0000000000	.....	.....	99	81	24	22	7.8	55	371	458	....	...	...	...	....	....	....	....	Epidemic encephalitis
110	5/13/25	11	200	7	0135521100	.....	.....	151	73	18	..	7.3	48	353	445	....	...	...	...	....	....	....	....	Cerebellar tumor
111†	5/13/25	11	670	0	0000000000	.....	.....	151	88	18	13	7.3	8	353	449	....	...	...	...	....	....	....	....	Cerebellar tumor
112	10/11/28	48	160	3	1111000000	.....	.....	94	63	..	..	7.3	42	378	444	....	...	297	306	9.35	4.4	....	....	Chronic epidemic encephalitis
113	11/ 7/28	66	...	..	.....	0.543	.....	104	..	25	..	6.3	..	380	441	....	...	321	325	8.0	....	....	....	Undiagnosed
329	11/18/27	30	60	4	.....	0.581	0.558	97	61	29	16	6.4	32	367	446	....	...	...	...	....	....	7.84	....	Pellagra
114	5/22/26	35	160	3	0000000000	.....	.....	86	62	20	18	7.9	22	382	448	....	...	...	...	9.48	4.6	....	....	Retrobulbar neuritis
169†	2/26/25	40	...	2	0000123221	.....	.....	98	65	20	..	7.4	66	357	419	....	...	...	...	....	....	....	....	Undiagnosed
115	10/26/28	42	370	4	1122210000	0.570	0.555	129	72	22	13	7.7	80	345	441	....	...	324	326	9.4	4.6	9.21	....	Cerebral hemorrhage
117	10/ 4/25	23	240	256	0011222110	.....	.....	...	66	22	12	7.8	86	350	435	....	...	...	...	....	....	....	....	Acute poliomyelitis
118	10/27/25	19	170	23	0000001000	.....	.....	124	51	17	12	8.2	93	353	439	....	...	...	...	....	....	....	....	Subarachnoid hemorrhage
Maximum						0.581	0.558	159	105	34	22	8.2	93	382	458	....	...	324	331	10.1	5.3	9.21		
Minimum						0.543	0.555	86	51	17	12	6.3	22	345	418	....	...	297	301	8.0	4.4	7.84		
Average						0.560	0.557	114	68	24	17	7.3	45	360	439	....	...	311	318	9.3	4.7	8.57		

* Fluid from the cisterna magna.
† Fluid from the lateral ventricle.

TABLE 7.—*Serum Protein Less Than 6 Gm. per Hundred Cubic Centimeters in Fasting Patients*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
119	2/13/29	48	150	2 *	0011110000	0.584	0.570	102	66	29	..	5.9	34	364	439	4.3	1.6	323	339	9.31	4.76	8.13	0.82	Multiple sclerosis
120	3/27/25	22	670+	3	0000120000	.....	.....	97	53	28	..	5.9	13	359	433	....	...	...	...	....	....	....	....	Extradural abscess
121	11/ 8/28	10	...	..	0123311000	0.535	0.538	135	68	30	16	5.8	46	354	430	....	...	305	309	7.05	3.95	7.71	....	Malignant endocarditis
122	3/19/25	51	125	0	0123210000	.....	.....	94	50	21	17	5.6	31	373	428	....	...	...	...	....	....	....	....	Nephrosis with edema
124	3/21/25	42	225	0	0021300000	.....	.....	98	59	23	..	4.8	7	348	427	....	...	...	...	....	....	....	....	Nephrosis with edema
125	7/30/25	32	110	1	0011100000	.....	.....	83	65	45	38	4.7	33	361	433	....	...	...	...	....	....	....	....	Nephrosis
Maximum						0.584	0.570	135	68	45	38	5.9	46	373	439	....	...	323	339	9.3	4.8	8.1		
Minimum						0.535	0.538	83	50	21	16	4.7	7	348	427	....	...	305	309	7.1	4.0	7.7		
Average						.....	.....	102	60	29	24	5.5	27	360	432									

TABLE 8.—*Patients with Normal Cerebrospinal Fluid—Serum Protein Not Determined*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
126	2/15/28	36	100	3	1122100000	0.578	0.583	98	65	26	..	...	38	364	439	2.9	1.3	330	343	9.62	4.75	8.28	1.08	Multiple sclerosis
127	12/16/26	27	160	2	1110000000	.....	.....	81	61	22	19	...	24	367	447	....	...	...	...	....	....	....	....	Chronic epidemic encephalitis
128	12/30/26	28	180	1	0122100000	.....	.....	...	..	..	..	...	38	373	435	....	...	...	...	....	....	....	....	Undiagnosed
129*	12/30/26	28	150	2	1122100000	.....	.....	...	..	..	..	...	18	373	435	....	...	...	...	....	....	....	....	Undiagnosed
130†	1/14/26	25	165	1	0000000000	.....	.....	98	63	19	..	...	45	351	431	....	...	...	...	....	....	....	....	Epilepsy
131	1/14/28	25	500	0	0000000000	.....	.....	154	90	..	..	...	21	367	439	....	...	...	...	10.89	....	....	....	Status epilepticus
132†	11/13/25	18	145	1	0000000000	.....	.....	110	71	22	..	...	17	348	435	....	...	...	...	....	....	....	....	Myasthenia gravis
133†	10/15/24	66	170	1	0011100000	.....	.....	125	76	39	21	...	24	385	450	....	...	...	...	....	....	....	....	Retrobulbar neuritis
313*	1/22/25	64	90	..	0000000000	.....	.....	97	67	..	..	...	19	381	459	....	...	...	...	....	....	....	....	Tumor of the spinal cord
Maximum								154	90	39	..	...	45	385	459									
Minimum								81	61	19	..	...	17	348	431									
Average								109	70	26	..	...	27	368	441									

* Fluid from the cisterna magna.
† Fasting less than nine hours.

TABLE 9.—*Patients with Minor Abnormalities in the Cerebrospinal Fluid—Serum Protein Not Determined*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
134†	2/ 2/25	20	250	..	0011210000	.....	.....	116	77	..	..	...	29	345	438	....	...	...	...	....	....	....	....	Otitis media
135†	5/ 9/25	58	220	1	0001100000	.....	.....	105	79	..	..	...	55	370	447	....	...	...	...	....	....	....	....	Acoustic neuroma
136†	10/16/24	66	110	2	0001111000	.....	.....	107	61	..	..	...	74	367	435	....	...	...	...	....	....	....	....	Acoustic neuroma
137†	1/ 6/25	40	210	..	0032100000	.....	.....	102	94	33	..	...	51	355	438	....	...	...	...	....	....	....	....	Undiagnosed
138†	1/21/25	24	140	19	0122110000	.....	.....	94	89	..	..	...	35	367	448	....	...	...	...	....	....	....	....	Epidemic encephalitis
139†	1/26/25	24	120	6	0000110000	.....	.....	89	62	..	..	...	47	358	446	....	...	...	...	....	....	....	....	Epidemic encephalitis
140†	8/18/25	36	160	2	0001000000	.....	.....	91	51	28	18	...	47	372	436	....	...	...	...	....	....	....	....	Multiple sclerosis
141†	1/29/25	27	140	9	0123200000	.....	.....	94	64	..	..	...	24	362	448	....	...	...	...	....	....	....	....	Undiagnosed
142†	12/ 3/24	28	...	..	1111000000	.....	.....	115	77	..	..	...	21	367	443	....	...	...	...	....	....	....	....	Brain tumor
143†	3/18/25	13	165	9	0000100000	.....	.....	112	64	22	..	...	30	357	439	....	...	...	...	....	....	....	....	Undiagnosed
144†	12/ 5/24	25	160	6	0011221100	.....	.....	121	83	29	14	...	40	361	434	....	...	...	...	....	....	....	....	Acute epidemic encephalitis
145†	1/11/26	30	100	24	1111110000	.....	.....	74	47	..	..	...	108	364	428	....	...	...	...	....	....	....	....	Syphilis of the central nervous system
146†	2/ 6/25	37	110	33	4555554322	.....	.....	146	63	..	..	...	138	351	420	....	...	...	...	....	....	....	....	Cerebellar abscess
147†‡	3/18/26	39	360	600	0000000000	.....	.....	107	65	32	25	...	89	350	433	....	...	...	...	....	....	....	....	Subarachnoid hemorrhage
148†§	2/ 4/25	44	100	12	0001232100	.....	.....	...	..	..	..	...	105	353	441	....	...	...	...	....	....	....	....	Undiagnosed*
149†	11/ 7/27	25	...	..	.....	.....	.....	103	59	31	18	...	129	348	441	....	...	...	...	....	....	....	....	Undiagnosed
150†	1/30/25	49	...	0	0124555422	.....	.....	158	..	..	..	...	118	347	436	....	...	...	...	....	....	....	....	Tumor of the brain
151	7/ 7/24	62	110	18	.....	.....	.....	101	57	45	30	...	111	362	436	....	...	...	...	....	....	....	....	Herpes zoster
209*†	1/ 6/26	59	130	..	0000000000	.....	.....	103	80	..	..	...	13	367	443	....	...	...	...	....	....	....	....	Tumor of the spinal cord
218*†	1/22/25	64	90	..	0000000000	.....	.....	97	67	..	..	...	19	381	459	....	...	...	...	....	....	....	....	Tumor of the spinal cord
123	10/15/28	31	125	3	0011100000	0.577	0.557	103	73	26	19	...	26	364	441	....	...	304	317	9.57	4.42	9.11	....	Chronic epidemic encephalitis
Maximum								158	94	45	30	...	138	381	459									
Minimum								74	47	22	14	...	13	345	420									
Average								107	69	30	20	...	63	358	439									

* Fluid from the cisterna magna.
† Fasting less than nine hours.
‡ 250,000 red blood cells in the spinal fluid.
§ 11,000 red blood cells in the spinal fluid.

TABLE 10.—*Normal Cerebrospinal Fluid in Fasting Patients with Serum Chloride Less Than 344 Mg. per Hundred Cubic Centimeters*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
152	12/16/28	60	60	0	1122210000	.....	.....	...	66	..	..	6.3	24	338	420	3.49	1.2	304	295	9.62	5.20	....	....	Pulmonary tuberculosis
153	9/24/27	65	150	29	.....	.....	.....	137	82	25	18	7.7	26	341	445	....	...	...	...	....	....	....	....	Undiagnosed
154	12/11/29	52	210	0	0000000000	.....	.....	99	58	25	14	6.1	16	332	418	....	...	...	...	....	....	8.16	0.95	Pulmonary tuberculosis
155	2/23/29	36	...	..	1111100000	.....	.....	...	52	19	..	6.6	12	343	423	4.6	...	285	322	8.9	4.6	8.90	1.26	Bronchiectasis
156	12/ 3/28	67	400	..	1111100000	.....	.....	104	57	43	28	6.9	21	341	436	....	...	313	343	....	....	....	....	Pulmonary tuberculosis
157	12/ 9/29	14	50	0	.....	0.537	0.538	80	47	26	12	6.4	18	341	420	....	...	306	317	....	....	8.06	0.89	Pulmonary tuberculosis
158	9/16/25	36	230	2	0000110000	.....	.....	107	64	15	..	8.0	44	325	413	....	...	...	...	....	....	....	....	Tumor of the brain
159*	9/16/25	36	...	..	.....	.....	.....	107	74	15	..	8.0	28	325	413	....	...	...	...	....	....	....	....	Tumor of the brain
160	12/16/29	25	140	0	0000000000	0.561	0.574	84	57	27	13	8.2	29	340	423	....	...	331	344	....	....	10.18	0.92	Pulmonary tuberculosis
161	5/21/25	17	600	230	0112210000	.....	.....	129	86	31	17	7.9	37	332	439	....	...	...	...	....	....	....	....	Abscess of the frontal lobe
162	12/30/28	38	110	3	0000000000	.....	.....	...	56	..	..	...	21	319	407	....	...	...	...	....	....	....	....	Pulmonary tuberculosis
328	7/10/25	37	140	0	0000000000	.....	.....	82	56	18	11	6.82	36	341	420	....	...	...	...	....	....	....	....	Glioma of the temporal lobe
Maximum								137	86	31	28	8.2	44	343	445	....	...	331	344	....	....	10.18	1.26	
Minimum								80	47	15	11	6.1	12	319	407	....	...	285	295	....	....	8.06	0.89	
Average								103	63	24	16	7.2	26	335	423	....	...	308	324	....	....	8.83	1.01	

* Fluid from the lateral ventricle.

TABLE 11.—*Slight Abnormalities in the Cerebrospinal Fluid of Fasting Patients with Serum Chloride Less Than 344 Mg. per Hundred Cubic Centimeters*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
170	9/14/25	31	70	6	1233210000	.....	.....	97	66	21	15	6.7	46	341	414	....	...	...	...	....	....	....	....	Multiple sclerosis
171	6/ 6/25	46	195	69	0000000000	.....	.....	119	77	44	39	7.0	50	293	404	....	...	...	...	....	....	....	....	Acute poliomyelitis
173	7/16/25	37	170	1	1111100000	.....	.....	120	70	29	16	6.8	87	344	420	....	...	...	...	....	....	....	....	Epidemic encephalitis
175*	10/ 1/28	43	330	8	0000000000	0.564	0.570	127	80	36	26	8.2	144	336	424	....	...	330	337	10.1	4.75	10.4	....	Undiagnosed
Maximum								127	80	44	39	8.2	144	344	424									
Minimum								97	66	21	15	6.7	46	293	404									
Average								116	73	33	24	7.2	82	329	416									

* Four thousand nine hundred red blood cells in the spinal fluid.

TABLE 12.—*Normal Cerebrospinal Fluid in Patients Not Fasting with Serum Chloride Less Than 344 Mg. per Hundred Cubic Centimeters*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
164	7/30/25	26	200	2	0111210000	.....	.....	78	67	29	11	7.1	44	341	429	....	...	...	...	....	....	....	....	Toxic labyrinthritis
165	7/ 9/25	43	80	1	0012211000	.....	.....	104	68	27	20	6.3	34	342	424	....	...	...	...	....	....	....	....	Multiple sclerosis
166	6/16/25	21	...	0	0000000000	.....	.....	116	85	37	25	7.2	24	312	414	....	...	...	...	....	....	....	....	Meningismus
167	12/26/25	38	130	5	0000000000	.....	.....	137	78	25	13	8.0	28	291	378	....	...	...	...	....	....	....	....	Diabetes with pneumonia
168	7/ 8/25	30	155	1	0000000000	.....	.....	93	78	26	20	7.0	19	323	410	....	...	...	...	....	....	....	....	Acute tonsilitis
Maximum								137	85	37	25	8.0	44	342	429									
Minimum								78	67	20	11	6.3	19	291	378									
Average								103	75	27	17	7.0	29	323	411									

TABLE 13.—*Slight Abnormalities in the Cerebrospinal Fluid of Patients (Not Fasting) Serum Chloride Less Than 344 Mg. per Hundred Cubic Centimeters*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
178	8/13/25	43	130	1	0011211000	.....	.....	100	64	20	19	7.0	48	326	418	....	...	...	...	....	....	....	....	Carcinoma of the nasopharynx
177	10/30/25	40	110	3	0011210000	.....	.....	93	87	21	14	7.1	52	341	422	....	...	...	...	....	....	....	....	Whooping cough; cerebral apoplexy
174	11/14/27	60	90	17	.....	.....	0.544	96	55	23	16	7.3	57	343	424	....	...	...	...	....	....	....	....	Syphilis of the central nervous system
186	7/10/25	44	110	..	0000110000	.....	.....	102	64	29	19	6.8	60	328	407	....	...	...	...	....	....	....	....	Duodenal ulcer
183	2/ 4/26	38	220	8	0000000000	.....	.....	91	67	21	16	7.4	66	342	427	....	...	...	...	....	....	....	....	Multiple sclerosis
176	10/ 6/25	23	320	198	0000122110	.....	.....	94	..	29	..	7.4	71	341	440	....	...	...	...	....	....	....	....	Acute poliomyelitis
181	6/ 5/25	46	140	80	0000000000	.....	.....	110	59	42	..	8.0	78	341	441	....	...	...	...	....	....	....	....	Anterior poliomyelitis
179	7/ 3/25	38	160	52	4554442210	.....	.....	114	70	20	19	7.0	82	344	430	....	...	...	...	....	....	....	....	Dementia paralytica
185*	8/ 4/25	12	100	18	0011210000	.....	.....	109	65	24	18	6.6	102	304	407	....	...	...	...	....	....	....	....	Anterior poliomyelitis
182	3/ 9/25	54	160	27	0000000000	.....	.....	152	77	39	21	7.0	103	344	422	....	...	...	...	....	....	....	....	Undiagnosed
184	10/ 5/25	17	95	170	1111223210	.....	.....	106	53	25	22	7.0	125	341	425	....	...	...	...	....	....	....	....	Anterior poliomyelitis
180†	6/ 8/25	24	...	450	0021110000	.....	.....	106	60	26	21	7.0	148	333	415	....	...	...	...	....	....	....	....	Fractured skull
Maximum								152	87	42	22	8.0	148	344	440									
Minimum								91	53	20	16	6.6	48	304	407									
Average								97	66	27	19	7.1	83	336	423									

* Two thousand two hundred and ninety-eight red blood cells in the spinal fluid.
† One hundred and eight thousand red blood cells in the spinal fluid.

* Two thousand two hundred and ninety-eight red blood cells in the spinal fluid.
† One hundred and eight thousand red blood cells in the spinal fluid.

TABLE 14.—*Patients with Serum Protein Under 6 Gm. per Hundred Cubic Centimeters and Serum Chloride Less Than 344 Mg. per Hundred Cubic Centimeters*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
187	12/17/29	56	80	0	0000000000	0.536	0.537	83	56	29	14	5.1	13	306	383	....	...	274	288	....	....	6.28	0.83	Pulmonary tuberculosis
188	3/ 5/25	20	200	8	1335542100	.....	.....	94	56	29	19	4.6	7	324	406	....	...	...	...	....	....	....	....	Nephrosis
189	7/17/25	37	205	30	0001111000	.....	.....	76	54	29	22	6.0	53	318	388	....	...	...	...	....	....	....	....	Vascular hypertension
190	5/29/25	25	200	78	0000121100	.....	.....	111	56	15	..	6.0	77	342	413	....	...	...	...	....	....	....	....	Malignant endocarditis
191*	5/29/25	25	295	70	0000022210	.....	.....	111	57	..	..	6.0	114	342	416	....	...	...	...	....	....	....	....	Malignant endocarditis
192†	9/12/28	75	50	5	0001110000	.....	.....	...	59	35	..	5.7	105	325	388	....	...	312	304	6.75	3.38	....	....	Pulmonary tuberculosis
312‡	8/ 3/25	48	160	0	1222211000	.....	.....	110	65	30	15	4.2	114	344	425	....	...	...	...	....	....	....	....	Glioma of cerebrum
Maximum								111	65	35	22	6.0	114	344	425									
Minimum								76	54	15	14	4.2	7	306	383									
Average								98	58	28	17	5.4	69	329	403									

* Fluid from the lateral ventricle.
† Five thousand red blood cells in the spinal fluid.
‡ Fasting less than nine hours.

TABLE 15.—*Patients with Serum Chloride Less Than 344 Mg. per Hundred Cubic Centimeters and Serum Protein Not Determined*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
196‡	2/ 5/25	7	400	2	0000000000	.....	.....	179	84	..	..	...	15	318	387	....	...	...	...	....	....	....	....	Streptococcus septicemia
199‡	1/12/25	5	180	8	0000000000	.....	.....	89	60	..	..	...	19	339	443	....	...	...	...	....	....	....	....	Undiagnosed
193‡	4/ 9/25	22	115	4	0000000000	.....	.....	104	64	..	..	...	27	342	427	....	...	...	...	....	....	....	....	Undiagnosed
197	9/19/28	27	110	2	0011100000	.....	.....	141	76	..	..	...	33	312	401	....	...	298	308	8.3	3.8	10.16	....	Pulmonary tuberculosis
194‡	1/23/25	37	...	..	0001100000	.....	.....	106	85	..	..	...	37	339	439	....	...	...	...	....	....	....	....	Undiagnosed
195*‡	1/23/25	37	...	..	0001110000	.....	.....	106	96	..	..	...	26	339	439	....	...	...	...	....	....	....	....	Undiagnosed
198‡	2/ 5/25	27	90	7	0001211000	.....	.....	...	..	..	..	...	40	326	416	....	...	...	...	....	....	....	....	Hysteria
201‡	3/ 2/26	7	...	442	0001110000	.....	.....	125	74	..	..	...	44	321	420	....	...	...	...	....	....	....	....	Polycythemia
200‡	10/14/24	48	65	0	0000000000	.....	.....	102	55	..	..	...	48	341	413	....	...	...	...	....	....	....	....	Pernicious anemia
203†‡	2/ 2/25	49	...	30	0223211000	.....	.....	...	..	..	..	...	86	333	431	....	...	...	...	....	....	....	....	Tumor of the brain
202‡	2/ 2/25	49	...	16	0011231100	.....	.....	...	..	..	..	...	118	333	425	....	...	...	...	....	....	....	....	Tumor of the brain
204‡	12/ 3/24	59	...	..	5532210000	.....	.....	121	60	..	..	...	168	331	401	....	...	...	...	....	....	....	....	Fractured skull; cerebral hemorrhage
Maximum								179	96	..	..	...	168	342	443									
Minimum								89	55	..	..	...	15	312	387									
Average								119	73	..	..	...	55	331	420									

* Fluid from the cisterna magna.
† Fluid from the lateral ventricle.
‡ Fasting less than nine hours.

TABLE 16.—*Patients with Cerebrospinal Fluid Protein Above 200 Mg. per Hundred Cubic Centimeters*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
206§	10/21/25	16	110	..	0000111110	.....	.....	92	60	21	16	7.1	225	355	436	....	...	...	...	....	....	....	....	Anterior poliomyelitis
207§	10/29/24	17	160	21	0012231100	.....	.....	101	65	..	..	...	228	341	420	....	...	...	...	....	....	....	....	Anterior poliomyelitis
208†§	10/ 2/28	42	500	18	1000000000	0.548	0.539	136	77	26	17	7.6	236	333	388	....	...	319	327	9.4	4.68	9.33	....	Cerebral hemorrhage
209§	1/ 6/26	59	220	..	0022223334	.....	.....	103	71	..	..	...	279	367	439	....	...	...	...	....	....	....	....	Tumor of the spinal cord
210§	6/16/25	60	...	..	0000001100	.....	.....	...	..	..	..	...	258	319	401	....	...	...	...	....	....	....	....	Cerebral hemorrhage
211*§	6/16/25	60	...	..	0000000000	.....	.....	...	..	..	..	...	288	319	414	....	...	...	...	....	....	....	....	Cerebral hemorrhage
212§	4/17/25	43	160	1	2222333100	.....	.....	103	59	24	19	7.1	348	364	428	....	...	...	...	....	....	....	....	Multiple neuritis
213§	2/26/25	40	...	2	0001222232	.....	.....	98	61	20	..	7.4	414	357	419	....	...	...	...	....	....	....	....	Undiagnosed
214§	12/ 2/26	33	130	3	1111210000	.....	.....	130	..	29	..	7.8	438	364	432	....	...	...	...	....	....	....	....	Tumor of the spinal cord
215‡	1/25/29	44	240	8	1111223222	0.583	0.561	126	86	42	29	5.6	480	356	433	5.6	2.1	294	321	8.52	4.83	7.48	1.15	Undiagnosed
216	1/ 8/30	25	140	5	0000001223	.....	.....	145	83	19	15	7.0	900	319	383	....	...	305	315	....	....	8.71	1.77	Multiple neuritis; syphilis
217§	1/16/25	64	50	24	0111113221	.....	.....	...	..	..	..	...	930	395	456	....	...	...	...	....	....	....	....	Tumor of the spinal cord
218§	1/22/25	64	...	330	0001222223	.....	.....	97	..	..	..	...	2084	381	447	....	...	...	...	....	....	....	....	Tumor of the spinal cord
Maximum								145	86	42	29	7.6	2084	395	447									
Minimum								92	59	19	15	5.6	225	319	383									
Average								113	70	26	19	7.1	546	352	423									

* Fluid from the lateral ventricle.
† Eight thousand nine hundred and thirty red blood cells in the spinal fluid.
‡ Two thousand four hundred and forty-eight red blood cells in the spinal fluid.
§ Fasting less than nine hours.

TABLE 17.—*Patients with Serum Non-Protein Nitrogen Over 45 Mg. per Hundred Cubic Centimeters*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point, —° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
219	10/ 9/28	48	170	2	0000000000	0.534	0.534	148	92	48	29	6.4	16	290	406	....	...	260	286	10.52	5.2	8.26	....	Pulmonary tuberculosis
220	9/24/28	50	60	3	.....	0.608	0.571	164	98	52	31	4.7	20	302	427	....	...	312	326	....	....	7.54	....	Pulmonary tuberculosis
221§	11/ 9/25	60	...	2	0000000000	.....	.....	105	64	55	45	6.4	28	346	426	....	...	...	...	....	....	....	....	Lead poisoning
222†§	1/21/29	50	110	45	0000000000	0.596	0.597	108	82	60	48	7.3	41	351	439	3.9	...	327	333	9.0	4.2	10.7	1.02	Undiagnosed
223§	4/22/25	13	280	1	0000000000	.....	.....	122	76	62	47	6.1	13	359	442	....	...	...	...	....	....	....	....	Nephritis
224§	12/11/20	9	210	+	4454321000	.....	.....	122	136	64	43	...	26	376	454	....	...	...	...	....	....	....	....	Nephritis
225§	3/ 4/26	65	60	6	0000011000	.....	.....	142	77	66	56	8.1	42	308	419	....	...	...	...	....	....	....	....	Septicemia; pneumonia
226	3/28/27	43	290	30	1222100000	.....	.....	114	82	67	39	7.1	53	348	435	....	...	...	...	....	....	....	....	Chronic nephritis
227§	10/19/26	59	40	10	1111000000	.....	.....	174	103	68	64	8.2	31	365	459	....	...	...	...	....	....	....	....	Undiagnosed
228§	12/19/27	49	...	..	.....	.....	.....	...	..	69	51	...	59	362	451	....	...	...	...	....	....	....	....	Uremia
229†§	6/27/25	13	180	36	1111230000	.....	.....	109	79	75	..	6.5	31	368	441	....	...	...	...	....	....	....	....	Undiagnosed
230§	4/28/26	19	180	0	0001110000	.....	.....	141	68	76	17	9.6	26	327	433	....	...	...	...	10.33	5.23	....	....	Epilepsy
231§	2/ 3/25	11	...	2	0122100000	.....	.....	186	81	83	64	5.7	10	365	431	....	...	...	...	....	....	....	....	Nephritis
232§	10/10/24	42	260	3	5554321000	.....	.....	162	112	112	90	...	17	353	454	....	...	...	...	....	....	....	....	Nephritis
233§	4/ 6/25	41	...	3	2222343110	.....	.....	169	115	135	125	6.6	77	298	430	....	...	...	...	....	....	....	....	Uremia
234§	12/19/24	33	370	2	0111211300	.....	.....	168	99	143	107	...	31	285	402	....	...	...	...	....	....	....	....	Uremia
235‡§	10/20/24	41	210	10	0123211100	.....	.....	151	78	159	131	...	60	376	465	....	...	...	...	....	....	....	....	Uremia
236§	8/25/25	50	400	32	0000011000	.....	.....	...	90	295	258	...	76	351	465	....	...	...	...	....	....	....	....	Uremia
Maximum						0.608	0.597	186	136	295	258	9.6	77	376	465	....	...	327	333	10.5	5.2	10.7	....	
Minimum						0.534	0.534	105	64	48	17	4.7	10	285	402	....	...	260	286	9.0	4.2	7.5	....	
Average						0.579	0.567	143	90	94	73	6.9	37	341	438	....	...	300	315	9.9	4.9	8.6	....	

* Two hundred and seventy-five red blood cells in the spinal fluid.
† Four thousand five hundred red blood cells in the spinal fluid.
‡ Ninety-seven red blood cells in the spinal fluid.
§ Fasting less than nine hours.

COMMENT

No attempt will be made in this paper to review the extensive literature on the chemistry of the cerebrospinal fluid. This has been covered adequately in a recent monograph by Walter.[17]

The only important series of determinations on normal human cerebrospinal fluid are the thirty-eight cases reported by Mestrezat, in 1912.[1] In these cases cerebrospinal fluid was obtained from patients fasting over night who were about to undergo an operation under spinal anesthesia. The patients were chosen particularly to represent the normal state. For instance, seventeen were being operated on for hernia and three for chronic appendicitis. In addition, Mestrezat gave analyses of a mixture of twenty other similar fluids from normal patients. These analyses probably constitute the most important data on the normal cerebrospinal fluid in the literature.

The values obtained by Mestrezat for freezing point, protein, sugar and chloride are essentially those recognized as normal today. They are: freezing point, from —0.57 to —0.59 C., average —0.58 (five determinations); "albumin," from 6 to 33 mg. per hundred cubic centimeters, average 18.6 (twenty-nine determinations); chloride (expressed as sodium chloride), from 721 to 740 mg. per hundred cubic centimeters (one case, 760), average 732 (27 determinations); sugar, from 50 to 62 mg. per hundred cubic centimeters (one case, 42), average 53.5 (eleven determinations). Mestrezat gave no data on the blood in these cases.

Clinical diagnosis is usually incomplete and often erroneous. Even postmortem examination may fail to show the abnormalities responsible for variations in the composition of the fluids of the body. Rapid and significant changes may occur as the result of vomiting, diarrhea, food or fluid intake, or transient changes in kidney function. Thus, for the study of the equilibrium between cerebrospinal fluid and blood plasma, factors such as those mentioned are often of greater significance than either clinical or autopsy diagnosis. Most of the patients we have studied had abnormalities of one kind or another. Unless the diagnosis could be made with assurance, we have marked the cases "undiagnosed." It is our purpose to demonstrate the composition of the cerebrospinal fluid in relation to a given composition of plasma, rather than the composition of the cerebrospinal fluid in relation to a given disease. Therefore we have divided our cases into groups according to the composition of the blood and the degree of abnormality in the cerebrospinal fluid.

Since the level of every known substance in the cerebrospinal fluid, with the exception of protein, is dependent to some extent on its level in the plasma, it follows that any series of the "normal" cerebrospinal

17. Walter, F. K.: Die Blut-Liquorschranke, Leipzig, Georg Thieme, 1929.

fluids should include only cases in which the blood plasma is known to be normal with respect to each substance studied in the cerebrospinal fluid. For instance, it is futile to define the normal limits of sugar in the cerebrospinal fluid unless the sugar content of the blood plasma is known to be within certain limits. When the composition of the blood changes in respect to sugar, chloride, etc., the cerebrospinal fluid reflects this change after a latent period. After such change in the blood, it may be several hours before the lumbar cerebrospinal fluid again reaches equilibrium. Since the exact limits of this latent period are unknown and undoubtedly vary for different conditions, we need, for an accurate comparison of cerebrospinal fluid and plasma, assurance that the composition of the plasma has not changed during the interval between the formation of the fluid in the ventricles and its removal from the lumbar subarachnoid space. We believe that preceding lumbar puncture, a nine to twelve hour fast, with the patient in bed, gives reasonable assurance of equilibrium between blood and cerebrospinal fluid. It must be recognized, however, that changes in the composition of the blood plasma may occasionally take place from unknown causes even during fasting. These important factors have been neglected by most investigators.

In 122 instances the spinal fluid and blood were obtained in patients after an overnight fast (nine hours or more) in bed in the hospital. In 22 of these cases (table 1), although the patients were suffering from a variety of diseases, the spinal fluids were "normal," i. e., the pressure was not over 200 mm. of spinal fluid, the cell count not over 5 per cubic millimeter, the protein not over 45 mg. per hundred cubic centimeters, the colloidal gold reaction showed no change greater than a "2," and the Wassermann reaction was negative. In addition, the freezing-point depressions of serum and cerebrospinal fluid (determined in twelve cases in this group) were identical within 0.005 C. In this group the composition of the plasma was "normal" according to the following criteria: the sugar was not over 125 mg. per hundred cubic centimeters, the nonprotein nitrogen was not over 45 mg., the protein ranged between 6 and 8.2 Gm., the chloride ranged between 345 and 376 mg. per hundred cubic centimeters (from 570 to 620 expressed as sodium chloride) and the Wassermann reaction of the blood was negative.

This small group of "normal" cases, we believe, characterizes the equilibrium between human cerebrospinal fluid and plasma in regard to the substances studied. Whether any significant deviations from our figures occur in entirely healthy persons can be determined only when data on such cases are at hand.

In table 2 fifteen cases show increased cerebrospinal fluid pressure, i. e., over 200 mm. of spinal fluid. In all other respects the spinal fluid and plasma in these cases were "normal" according to the criteria for

table 1. We found no evidence to indicate that increased intracranial pressure alone modifies appreciably the distribution of any substance between the plasma and the cerebrospinal fluid.

In table 3 are forty-three cases under the same criteria of normality as those in table 1 as far as the plasma is concerned, but all showing one or more of the following abnormalities in the cerebrospinal fluid: pressure over 200 mm. of spinal fluid, cell count up to 35 per cubic millimeter, colloidal gold reaction abnormal and spinal fluid protein up to 132 mg. per one hundred cubic centimeters (in only the last five cases was the spinal fluid protein over 80 mg. per hundred cubic centimeters). In sixteen of these cases the freezing point depression in the cerebrospinal fluid differed from that of the plasma by from 0.007 to 0.025 C. These fifty-eight cases (tables 2 and 3) show but minor variations from the "normal" group in table 1.

Since the composition of the cerebrospinal fluid is not appreciably affected by increased intracranial pressure (table 2) or by minor abnormalities in the cerebrospinal fluid (table 3), the eighty cases included in tables 1, 2 and 3 give the range of composition of the cerebrospinal fluid for a given "normal" range of composition of the blood plasma.

It is also evident from the data presented in this paper that variations in the freezing-point depression, sugar, nonprotein nitrogen, chloride or sodium of the blood plasma are reflected in the cerebrospinal fluid. How far the distribution of sodium and of chloride ions between the blood plasma and the cerebrospinal fluid may be explained by the Donnan membrane equilibrium will be considered in a subsequent paper.

Table 5 consists of eighteen cases having the same criteria as for table 1, except that the patients were fasting less than nine hours before lumbar puncture and that in two instances the pressure of the spinal fluid was over 200 mm. of water.

The remaining cases are similarly grouped in tables according to the criteria described in their respective legends.

The data presented in this paper will be analyzed with special reference to the distribution of a particular substance such as sugar, chloride, etc., between the blood and the cerebrospinal fluid, in a series of separate communications. Here we shall call attention only to the fact that with the exception of sodium, which varies more in the cerebrospinal fluid than in the serum, the average range of variation for any substance in the cerebrospinal fluid is equal to or less than its range in the blood serum. This is true also for the total osmotic pressure. In the fifty-eight fasting patients for whom the freezing point was determined in both serum and cerebrospinal fluid, the maximum value in the serum was —0.608 degrees and in the cerebrospinal fluid —0.603

degrees; the minimum value in the serum —0.534 degrees and in the spinal fluid —0.534 degrees.

Claude Bernard [18] was the first to call attention to the constancy of the internal environment, referring in particular to the blood plasma. Cannon,[19] in a recent article, again brought this concept to the foreground. The true "milieu intérieur," however, is not the plasma but the intercellular fluid, a protein-free filtrate of the plasma, escaping through the capillary walls and bathing the tissue cells. If, as we believe, the cerebrospinal fluid is one example of this "milieu intérieur," the fact that this fluid has a constancy of composition as great as or even greater than that of the plasma is entirely consistent with the ideas of Claude Bernard.

SUMMARY

Comparative data are presented on simultaneous samples of venous blood plasma or serum and cerebrospinal fluid in 240 instances.

The cerebrospinal fluid of human beings is in osmotic equilibrium with the blood plasma and has a constancy of composition as great as that of the blood plasma.

18. Bernard, Claude: Léçons sur les phénomènes de la vie, Paris, J. B. Bailliere et fils, 1879, p. 5.

19. Cannon, W. B.: Sympathetic Division of Autonomic System in Relation to Homeostasis, Arch. Neurol. & Psychiat. **22**:282 (Aug.) 1929.

THE EQUILIBRIUM BETWEEN CEREBROSPINAL FLUID AND BLOOD PLASMA

II. THE COMPOSITION OF THE HUMAN CEREBROSPINAL FLUID AND BLOOD PLASMA IN MENINGITIS *

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In this paper we present a comparative study of the sugar, nonprotein nitrogen, chloride [1] and protein in parallel samples of blood plasma or serum and cerebrospinal fluid, in eighty-nine instances, on fifty patients, ranging in age from 2½ to 65 years. In addition, the freezing point depression, sodium, calcium, phosphorus and total solids have been determined in some of the cases. The methods used were described in the first paper of this series.[1a]

In table 1 are thirty instances of such parallel examinations in cases of tuberculous meningitis, in all of which the diagnosis was proved by autopsy, by guinea-pig inoculation of the cerebrospinal fluid or by finding tubercle bacilli in the cerebrospinal fluid by smear.

Table 2 is made up of eight instances of meningococcus meningitis, table 3 of eight instances of pneumococcus meningitis, table 4 of seven instances of streptococcus meningitis, table 5 of ten instances of syphilitic meningitis, table 6 of fifteen comparative studies on one patient with *Bacillus coli* meningitis, who recovered after more than four weeks

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1. Chloride values are commonly but incorrectly expressed as sodium chloride. In this and the preceding paper we have expressed these values as the chloride actually determined. They may be converted to the corresponding sodium chloride values by multiplying by the factor 1.65.

1a. Fremont-Smith, F.; Dailey, M. E.; Merritt, H. H.; Carroll, M. P., and Thomas, G. W.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma: I. The Composition of the Human Cerebrospinal Fluid and Blood Plasma, Arch. Neurol. & Psychiat., this issue, p. 1271.

TABLE 1.—*Tuberculous Meningitis*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point — ° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.	
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid
237*	12/ 9/24	22	390	41	0111111000	.....	.....	178	71	..	..	...	19	347	422	...	...	...	...	....	....	....	....
238	12/31/24	42	...	400	0011233322	.....	.....	110	30	38	24	...	144	307	388	...	...	...	...	....	....	....	....
239†	2/ 6/25	2½	...	251	.....	.....	.....	107	18	..	..	...	251	237	358	...	...	...	...	....	....	....	....
240‡	3/10/25	3	300 +	240	2222233422	.....	.....	88	32	..	..	...	160	312	362	...	...	...	...	....	....	....	....
241	4/13/25	29	425	64	0001111000	.....	.....	101	20	25	..	7.4	182	314	378	...	...	...	...	....	....	....	....
242	4/15/25	29	360	35	0012231110	.....	.....	113	20	..	..	...	190	293	342	...	...	...	...	....	....	....	....
243	4/16/25	29	290	49	.....	.....	.....	...	..	..	..	...	190	312	324	...	...	...	...	....	....	....	....
244	4/28/25	22	260	189	0012322111	.....	.....	107	29	..	..	...	138	266	405	...	...	...	...	....	....	....	....
245	5/ 1/25	22	...	180	0012331111	.....	.....	...	..	..	..	...	167	341	407	...	...	...	...	....	....	....	....
246	5/ 7/25	22	530	1,017	1222343321	.....	.....	168	15	38	..	8.2	286	344	399	...	...	...	...	....	....	....	....
247	5/29/25	31	160	108	0001222000	.....	.....	105	41	24	..	6.9	93	324	411	...	...	...	...	....	....	....	....
248	6/ 2/25	31	220	73	0011321000	.....	.....	110	28	25	..	6.4	133	325	402	...	...	...	...	....	....	....	....
249	6/13/25	31	600	177	0000111100	.....	.....	109	23	..	..	...	211	261	313	...	...	...	...	....	....	....	....
250	6/15/25	31	350	160	0000012110	.....	.....	159	27	28	..	6.7	296	261	312	...	...	...	...	....	....	....	....
251	7/13/25	14	110	24	0000100000	.....	.....	98	26	27	..	6.6	74	309	385	...	...	...	...	....	....	....	....
252	7/15/25	26	270	298	0111232110	.....	.....	116	46	27	23	7.6	213	287	355	...	...	...	...	....	....	....	....
253	7/21/25	26	380	376	0011222110	.....	.....	115	22	30	20	6.7	156	323	355	...	...	...	...	....	....	....	....
254	10/26/25	24	...	...	0001113221	.....	.....	111	22	28	26	6.8	206	307	357	...	...	...	...	....	....	....	....
255	10/28/25	24	430	54	0000112311	.....	.....	105	21	..	..	...	279	295	341	...	...	...	...	....	....	....	....
256	2/20/26	24	350	101	0000011121	.....	.....	122	23	34	26	8.0	178	331	391	...	...	...	...	....	....	....	....
257	9/21/27	43	...	...	.....	.....	.....	152	14	42	30	...	108	331	399	...	...	...	...	....	....	....	....
258	9/22/27	43	...	...	.....	.....	.....	131	22	53	28	...	100	370	413	...	...	...	...	....	....	....	....
259	9/23/27	43	...	...	.....	.....	.....	240	25	55	43	8.1	84	368	444	...	...	...	...	....	....	....	....
260	10/ 6/27	22	300 +	...	.....	.....	.....	142	18	55	42	7.0	324	326	368	...	...	...	...	....	....	....	....
261	10/ 7/27	22	...	...	.....	.....	.....	157	11	43	..	6.6	330	319	356	...	...	...	...	....	....	....	....
262	10/ 7/27	53	...	...	.....	.....	.....	96	30	31	23	7.6	216	284	335	...	...	...	...	....	....	....	....
263	11/ 7/27	50	450	...	.....	.....	.....	...	11	..	..	...	306	298	341	...	...	...	...	....	....	....	....
264	11/ 9/27	31	620	...	.....	0.530	.....	152	23	27	18	...	412	333	381	...	...	...	...	....	....	....	....
265§	11/10/27	31	...	186	.....	0.525	0.519	123	11	24	17	7.5	168	328	376	8.6	...	...	...	....	....	....	....
266	7/10/29	35	...	...	0012333211	.....	.....	...	5	..	..	...	160	314	345	...	...	282	304	....	....	....	....
	Maximum							240	71	55	43	8.2	412	370	444								
	Minimum							88	5	24	17	6.4	19	237	312								
	Average							128	24	34	27	7.2	192	312	372								

* Fluid from the cisterna magna.
† Forty-one red blood cells in the spinal fluid.
‡ One hundred red blood cells in the spinal fluid.
§ Five hundred and nineteen red blood cells in the spinal fluid.

TABLE 2.—*Meningococcus Meningitis*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point — ° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.	
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid
267	8/ 5/25	11	...	227	0000120000	.....	.....	132	79	..	..	...	84	305	381	...	...	...	...	....	....	....	....
268	10/13/25	44	170	1,700	.....	.....	.....	101	33	20	..	7.0	240	338	401	...	...	...	...	....	....	....	....
269	10/14/25	44	120	430	4444422233	.....	.....	125	44	21	..	7.5	429	341	414	...	...	...	...	....	....	....	....
270	10/19/25	44	...	...	.....	.....	.....	101	34	23	..	6.5	525	338	405	...	...	...	...	....	....	....	....
271	12/ 2/25	54	200	2,400	0000001100	.....	.....	112	15	..	..	...	429	321	364	...	...	...	...	....	....	....	....
272	11/16/28	29	...	...	1222235433	0.524	0.526	114	46	60	15	6.2	320	303	382	...	...	299	307	....	....	8.40	1.39
273	11/19/28	49	250	1,020	5555523344	0.555	0.527	110	27	30	18	6.2	1,998	322	393	...	...	296	303	....	....	8.18	2.03
314	12/17/25	40	260	1,139	0000012111	.....	.....	122	63	44	..	6.6	124	339	428	...	...	...	...	....	....	....	....
	Maximum							132	79	60	..	7.5	1,998	341	428								
	Minimum							101	15	20	..	6.2	84	303	381								
	Average							115	43	33	..	6.7	519	326	396								

TABLE 3.—*Pneumococcus Meningitis*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid*	Cells	Colloidal Gold	Freezing Point — ° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.	
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid
274	5/ 4/25	41	...	3,200	1111123332	.....	.....	149	8	29	..	6.6	380	316	369	...	...	...	...	....	....	....	....
275	4/ 2/26	22	350	1,300	1111121122	.....	.....	180	7	..	..	...	348	318	384	...	...	...	...	....	....	....	....
276	4/22/26	50	350	4,800	0000012332	.....	.....	208	..	25	..	8.7	135	199	340	...	...	...	...	....	....	....	....
277	4/ 5/28	15	...	10,000	.....	.....	.....	226	94	..	..	...	666	303	408	...	...	...	...	....	....	....	....
278	1/22/29	65	...	3,636	.....	0.616	0.607	187	10	39	25	5.8	1,332	372	410	3.7	1.9	323	341	7.8	....	7.89	2.04
279	1/29/29	47	680	2,675	0000023333	0.576	0.580	124	9	36	29	4.7	1,140	341	393	3.7	1.6	329	317	9.4	5.3	....	....
280*	1/29/29	47	250	1,064	0000133321	0.576	0.583	124	10	36	27	4.7	960	341	404	3.7	1.5	329	334	9.4	5.06	....	....
281	2/10/25	11	...	2,100	0001222110	.....	.....	...	33	..	..	...	66	322	399	...	...	...	...	...	....	....	....
	Maximum					0.616	0.607	226	94	39	29	5.8	1,332	372	410	3.7	1.9	329	341	9.4			
	Minimum					0.576	0.580	124	7	25	25	4.7	66	199	340	3.7	1.5	323	317	7.8			
	Average					0.589	0.590	179	24	23	27	5.1	628	312	388	3.7	1.7	327	331	8.9			

* Fluid from the cisterna magna.

* Fluid from the cisterna magna.

TABLE 4.—*Streptococcus Meningitis*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point — ° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.	
												Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.										
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid			Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid
282	2/12/25	30	...	.....	0011222354	.....	.....	195	13	43	..	7.1	800	358	371	...	...	...	...	....	....	....	....
283*	2/12/25	30	...	.....	0123221100	.....	.....	195	130	..	..	7.1	21	358	435	...	...	...	...	....	....	....	....
284	5/26/25	17	750+	9,000	0012344110	.....	.....	141	44	31	24	7.4	133	336	413	...	...	...	...	....	....	....	....
285	5/27/25	17	670+	11,000	0000144454	.....	.....	159	26	25	17	7.3	111	322	395	...	...	...	...	....	....	....	....
286	5/29/25	17	500	60,000	0001233211	.....	.....	123	31	23	17	7.3	78	311	395	...	...	...	...	....	....	....	....
287	6/ 1/25	17	...	7,440	0000022210	.....	.....	121	13	28	18	6.8	114	307	378	...	...	...	...	....	....	....	....
288	6/ 1/29	30	400	.....	0011123322	0.501	0.490	204	41	27	17	6.3	249	308	364	...	...	298	300	....	....	8.71	1.25
	Maximum							204	130	43	24	7.4	800	358	435								
	Minimum							121	13	23	17	6.3	21	307	364								
	Average							162	420	29	18	7.0	215	325	393								

* Fluid from lateral ventricle.

TABLE 5.—*Syphilitic Meningitis*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point — ° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.	
												Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.										
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid			Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid
291	2/ 3/25	36	250	1,133	0011121000	.....	.....	120	39	..	..	...	90	335	425	...	...	...	...	....	....	....	....
292	9/14/25	51	420	45	2223321000	.....	.....	103	18	22	20	7.1	105	345	401	...	...	...	...	....	....	....	....
293†	9/14/25	51	...	...	2332210000	.....	.....	103	68	..	..	7.1	6	345	420	...	...	...	...	....	....	....	....
294	1/11/26	30	100	24	1111110000	.....	.....	74	47	..	..	...	108	364	428	...	...	...	...	....	....	....	....
295	5/12/25	31	...	361	4555555532	.....	.....	...	..	30	..	7.6	129	346	431	...	...	...	...	....	....	....	....
296	4/ 9/26	31	...	110	4454443332	.....	.....	94	35	23	..	7.4	160	348	416	...	...	...	...	....	....	....	....
297	4/13/26	31	200	240	5442333432	.....	.....	85	..	21	..	7.1	45	364	419	...	...	...	...	....	....	....	....
315	2/12/25	36	170	115	0122322100	.....	.....	...	..	..	..	6.1	20	359	441	...	...	...	...	....	....	....	....
205*	2/ 4/26	47	80	137	0001232211	.....	.....	...	..	19	13	...	111	342	418	...	...	...	...	....	....	....	....
116	5/ 7/26	57	100	123	2455555332	.....	.....	94	..	35	..	6.9	80	365	441	...	...	...	...	9.65	4.62	....	....
	Maximum							120	68	35		7.6	160	365	441								
	Minimum							74	18	19		6.1	6	335	401								
	Average							82	41	25		7.0	85	351	422								

† Fluid from the lateral ventricle.
† Fluid from the lateral ventricle.

TABLE 6.—*Colon Bacillus Meningitis*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point — ° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.	
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid
298	11/23/28	26	600	4,370	1111122110	0.546	0.540	153	16	23	18	6.2	222	349	410	2.5	1.6	300	302	8.77	5.26	8.26	1.35
299	11/24/28	..	...	1,410	1111222100	.....	.....	119	20	31	18	6.3	264	316	378	2.73	1.2	284	289	8.94	4.44	....	....
300	11/26/28	..	...	2,320	0011222100	0.537	0.532	111	9	26	15	7.1	...	318	383	...	1.9	295	310	9.36	5.06	8.75	1.1
301	11/27/28	..	...	.....	.....	0.570	0.541	126	11	35	25	6.3	318	335	383	...	...	303	311	....	....	8.6	1.27
302	11/28/28	..	...	.....	.....	0.595	0.557	121	38	25	19	6.6	162	319	410	...	...	302	319	....	....	8.45	1.02
303	11/30/28	..	...	.....	.....	0.629	0.542	118	52	21	19	6.6	...	339	408	3.7	1.9	311	317	9.2	5.08	8.25	1.06
304	12/ 4/28	..	...	67	000.221100	0.634	0.542	98	59	27	11	6.5	70	345	420	...	...	315	314	9.05	4.68	8.02	1.01
305	12/ 6/28	..	...	191	.....	0.577	0.577	123	70	25	22	6.8	142	354	430	4.08	1.75	317	313	9.50	4.67	....	....
306	12/ 7/28	..	...	.....	.....	0.552	0.528	115	41	17	15	6.5	112	338	407	...	...	284	307	....	....	8.27	1.02
307	12/10/28	..	...	.....	.....	0.580	0.541	140	60	17	16	5.9	800	330	383	3.46	...	309	309	8.40	5.04	8.32	....
308	12/13/28	..	...	291	0011121100	0.502	0.557	115	55	23	10	6.0	72	348	420	3.58	...	318	318	8.95	5.0	7.56	....
309	12/17/28	..	...	62	1222110000	0.567	0.547	...	..	..	..	6.1	...	341	428	3.8	1.5	314	316	9.7	5.4	8.14	0.94
310	12/19/28	..	...	.....	.....	0.566	.....	108	48	21	16	5.9	114	348	431	...	...	300	311	....	....	....	....
311	1/ 2/29	..	160	3	0001111000	0.594	.....	94	54	27	21	6.0	240	364	414	...	...	...	...	....	....	8.11	....
316	12/ 1/28	..	...	50	1112211000	.....	.....	134	50	24	16	...	123	345	414	...	...	...	...	....	....	....	....
	Maximum					0.634	0.577	153	70	35	25	7.1	800	364	431	4.08	1.9	318	319	9.7	5.4	8.75	1.35
	Minimum					0.537	0.529	94	9	17	10	5.9	70	316	378	2.5	1.2	284	289	8.40	4.44	7.56	0.94
	Average					0.578	0.546	120	42	25	17	6.4	220	339	408	3.26	1.6	304	311	9.10	4.96	8.25	1.09

TABLE 7.—*Miscellaneous Cases*

Case	Date	Age	Pressure, Mm. Cerebrospinal Fluid	Cells	Colloidal Gold	Freezing Point — ° C.		Sugar, Mg. per 100 Cc.		Nonprotein Nitrogen, Mg. per 100 Cc.		Protein		Chloride, Mg. per 100 Cc.		Phosphorus, Mg. per 100 Cc.		Sodium, Mg. per 100 Cc.		Calcium, Mg. per 100 Cc.		Total Solids, Gm. per 100 Gm.		Diagnosis
						Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum, Gm. per 100 Cc.	Cerebrospinal Fluid, Mg. per 100 Cc.	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	Serum	Cerebrospinal Fluid	
289	6/14/26	48	456	...	0000110000	.....	.....	110	37	32	23	...	74	337	405	...	...	...	...	....	....	....	....	B. pyocyaneus meningitis
290	10/ 8/28	48	350	68	2223320000	0.535	0.490	144	39	28	25	7.0	190	301	351	...	...	295	306	9.45	4.83	8.54	....	Yeast meningitis
317	7/17/28	56	80	49	0000133321	.....	.....	129	68	37	32	6.3	334	354	418	...	...	...	...	....	....	....	....	Tuberculous meningitis ?
318	5/26/25	42	155	30	4545555555	.....	.....	92	47	27	17	7.0	296	348	415	...	...	...	...	....	....	....	....	Meningitis ?
319	6/15/26	34	200	315	0001233432	.....	.....	89	19	..	..	...	165	366	418	...	...	...	...	....	....	....	....	Aseptic meningitis
320	7/ 6/26	34	140	320	0145433100	.....	.....	85	..	22	20	...	133	364	435	...	...	...	...	....	....	....	....	Aseptic meningitis
321	6/16/26	12	640	47	0000111000	.....	.....	108	47	26	13	...	38	343	413	...	...	...	...	....	....	....	....	Aseptic meningitis
322	9/13/28	49	...	...	.....	.....	.....	...	33	..	..	...	...	271	383	...	...	308	320	....	....	....	....	Pulmonary tuberculosis, syphilitic meningitis
323*	9/17/28	49	110	20	2233210000	.....	.....	76	32	32	..	4.9	55	331	395	...	...	290	305	....	....	....	....	Pulmonary tuberculosis
324	8/11/25	40	190	6	0011123332	.....	.....	141	41	30	19	...	138	315	393	...	...	...	...	....	....	....	....	Acute osteomyelitis
325†	2/20/29	14	...	2,952	.....	0.578	0.583	100	19	19	16	6.2	156	355	422	...	...	332	343	....	....	8.83	1.19	Tumor of the brain
	Maximum							144	68	37	32	7.0	334	366	435			332	343					
	Minimum							76	19	19	13	4.9	38	271	383			290	305					
	Average							107	38	28	20	6.2	158	335	404			306	318					

* Five hundred and seventy red blood cells in the spinal fluid.

† Four thousand one hundred and forty red blood cells in the spinal fluid.

of nearly continuous drainage of the cerebrospinal fluid,[2] and table 7 of one case each of *Bacillus pyocyaneus* and yeast meningitis and of nine miscellaneous cases in some of which the diagnosis was less certain.

COMMENT

There is an extensive literature on the composition of the spinal fluid in meningitis. Particularly have the cells, protein, sugar and chloride been studied individually. There are almost no data, however, on the comparison between the chemistry of the plasma or serum and that of the cerebrospinal fluid in meningitis. Carmichael and Linder[3] gave detailed analyses in four cases.

The principal changes in the chemistry of the spinal fluid characteristic of all forms of acute meningitis, including tuberculous and acute syphilitic meningitis, are: (*a*) an increase in cells and protein and (*b*) a decrease in sugar and chlorides. In addition, in the few cases in which we have studied phosphorus and calcium we have found an increase in these substances, as was pointed out by Cohen.[4] We have also observed a decrease in sodium in a few cases. In the blood plasma the sugar is frequently increased, even though the patient may be fasting, and this increase is in marked contrast to the decrease in the sugar in the spinal fluid. It is striking evidence that the diminution of sugar in the spinal fluid is due to a local breaking down of the sugar. The chlorides in the blood plasma are nearly always decreased, and this decrease accounts in large part for the decrease in the chlorides in the spinal fluid in the majority of cases. This we have already pointed out.[5] Carmichael and Linder had similar results.[3] These changes in chlorides will form the subject of a separate communication. The values for sodium, calcium and phosphorus in the serum are usually below normal. The protein in the serum varies greatly in these cases, but in the majority it is within the normal range.

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2. This case will be reported separately.

3. Linder, G. C., and Carmichael, E. A.: Biochem. J. **22**:46, 1928.

4. Cohen, H.: Quart. J. Med. **17**:289, 1924.

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NONELECTROLYTES

THEIR DISTRIBUTION BETWEEN THE BLOOD AND THE CEREBROSPINAL FLUID *

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There are two theories as to the nature of the cerebrospinal fluid: one, that it is an active secretion; the other, that the fluid is a simple dialysate of the blood plasma formed by capillary pressure filtration. The evidence bearing on these two views has been reviewed by Fremont-Smith,[1] who came to the conclusion that there is no good evidence that the cerebrospinal fluid is a secretion and that the evidence as a whole is overwhelmingly in favor of dialysis. A good part of the evidence on which this conclusion is based comes from a study of the distribution of chlorides and other electrolytes between the plasma and the cerebrospinal fluid. If a simple membrane equilibrium does exist between the fluids, the distribution of ions between the two phases should follow the same physicochemical laws that have been shown to determine the distribution between the plasma and dialysates separated by a collodion or animal membrane.[2] For the most part, the evidence that is offered concerns the distribution of a single ion, and it is impossible to obtain certain data on the point in question except through an analysis of the total electrolyte system. On the other hand, with the organic substances or nonelectrolytes, such as urea or dextrose, there is no reason to suppose that any inequality in distribution between the plasma and cerebrospinal fluid should exist on the assumption that the latter is a filtration dialysate, except incident to the difference in the water content of the two fluids. It was the purpose of this investigation to study the distribution of various nonelectrolytes between the plasma and cerebrospinal fluid in man and in animals and the bearing of their distribution on the current theories of formation of the cerebrospinal fluid.

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* From the Department of Medicine, Stanford University Medical School.

1. Fremont-Smith, F.: Nature of Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **17**:317 (March) 1927.

2. Loeb, R. F.; Atchley, D. W., and Palmer, W. W.: J. General Physiol. **4**:591, 1921-1922. Hastings, A. B.; Salvesen, H. A.; Sendroy, J., Jr., and Van Slyke, D. D.: Ibid. **8**:701, 1927.

MATERIAL AND METHODS

Human material was obtained when cerebrospinal fluid was taken from the lumbar region in spinal punctures performed as a routine measure. Either a few minutes before or after this procedure, a specimen of venous blood was taken from a superficial vein in the arm and centrifugated immediately. In some cases serum was used for analysis and in others heparin plasma. In part, the specimens were taken from patients who had received intraspinal treatments for neurosyphilis. Since these results showed no significant variation from those obtained with fluid taken from normal subjects, one may conclude that neither the treatment nor the disease had an appreciable effect on the fluid.

Observations were also made on normal cats of various ages and both sexes. The effect of experimental uremia on the distribution of urea was also studied in these animals. In all cases, iso-amyl-ethyl barbituric acid, used as an anesthetic, was given intraperitoneally in a dose of from 3 to 4 cc. of a 2 per cent solution in sodium hydroxide per kilogram of body weight. There was no evidence that the drug influenced the concentration in the blood of the substances that were examined. Cerebrospinal fluid was taken from the cisterna magna, a flow of rapid drops being obtained. From 3 to 5 cc. was collected in from thirty to ninety minutes. A specimen of arterial blood, heparin being used as an anticoagulant, was obtained by puncture of the left side of the heart in the middle of the period of collection of the spinal fluid. Plasma was used for analysis, except in a few cases in which blood was taken without an anticoagulant, and the serum was used. The results were essentially the same. An experimental uremia was produced several hours after the first collection of fluid and blood by ligation of renal artery and entire pedicle of the kidney through a lumbar incision on either side.

All results are expressed on the basis of the concentration of the substance in question in the water of the cerebrospinal fluid and plasma or serum. The water content of these specimens was determined by drying a weighed sample to constant weight at 110 C. All samples used for analysis, whether directly or in the form of a tungstic acid filtrate, were measured by weight. Uric acid was determined according to the method of Folin,[3] the improved reagents[4] being used. A comparison with the isolation procedure[5] showed no appreciable change in the relative values from those obtained by the direct method. "Creatinine" was determined as whatever substance gave the chromogenic reaction with the alkaline picrate solution of Folin's method.[5] The concentrations of dextrose were obtained as the fermentable reducing substance by the gasometric ferri-cyanide method of Van Slyke and Hawkins.[6] Baker's yeast was used for the removal of the dextrose from the tungstic acid filtrate following the procedure described by Somogyi.[7] Urea was determined by a modified urease[8] method, the enzyme being used on the tungstic acid filtrates for human material and directly on the plasma and cerebrospinal fluid in the case of the cat specimens. The urea method was used successfully for over 200,000 determinations connected with experimental work and was

3. Folin, O.: J. Biol. Chem. **54**:153, 1922.
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5. Behre, J., and Benedict, S.: J. Biol. Chem. **52**:11, 1922.
6. Van Slyke, D. D., and Hawkins, J. A.: J. Biol. Chem. **79**:739, 1928.
7. Somogyi, M.: J. Biol. Chem. **75**:33, 1927.
8. Addis, T.: J. Lab. & Clin. Med. **10**:402, 1924.

TABLE 1.—*Distribution of Nonelectrolytes Between Human Plasma and Cerebrospinal Fluid Determined on a Basis of the Concentration of Water in Each Fluid*

	Uric Acid					Creatinine					Dextrose					Urea				
	Plasma		Cerebrospinal Fluid			Plasma		Cerebrospinal Fluid			Plasma		Cerebrospinal Fluid			Plasma		Cerebrospinal Fluid		
	Mg. per 100 Gm.	Mg. per 100 Gm. of Water	Mg. per 100 Gm.	Mg. per 100 Gm. of Water	Water Ratio	Mg. per 100 Gm.	Mg. per 100 Gm. of Water	Mg. per 100 Gm.	Mg. per 100 Gm. of Water	Water Ratio	Mg. per 100 Gm.	Mg. per 100 Gm. of Water	Mg. per 100 Gm.	Mg. per 100 Gm. of Water	Water Ratio	Mg. per 100 Gm.	Mg. per 100 Gm. of Water	Mg. per 100 Gm.	Mg. per 100 Gm. of Water	Water Ratio
1.....	6.26	6.91	1.68	1.70	0.246	1.27	1.40	0.59	0.60	0.429	118.8	131.1	27.7	28.1	0.214	21.91	24.17	8.88	8.98	0.316
2.....	5.08	5.52	0.91	0.92	0.166	1.34	1.46	0.96	0.97	0.657	73.3	79.7	64.7	65.4	0.821	17.58	19.12	4.59	4.64	0.242
3.....	3.82	4.18	2.78	2.81	0.672	3.22	3.52	1.33	1.34	0.381	133.3	145.8	65.5	66.2	0.454	27.80	30.39	6.23	6.29	0.207
4.....	3.64	4.07	0.95	0.96	0.236	1.43	1.57	1.05	1.06	0.675	.....	.....	....	....	.....	36.92	40.25	9.74	9.84	0.245
5*.....	2.80	2.93	1.40	1.41	0.483	1.88	1.97	1.91	1.93	0.980	135.4	141.8	32.2	33.7	0.238	11.21	11.74	4.76	4.80	0.411
6.....	5.55	6.06	2.53	2.56	0.425	1.27	1.39	1.12	1.13	0.814	.....	.....	....	....	.....	18.15	20.00	8.41	8.49	0.424
7*.....	4.70	5.14	2.21	2.23	0.434	1.73	1.89	1.39	1.44	0.743	.....	.....	....	....	.....	54.50	59.60	38.57	39.38	0.657
8*.....	4.06	4.44	1.84	1.86	0.418	1.40	1.53	1.10	1.11	0.726	94.0	102.8	62.9	63.5	0.676	27.13	29.80	8.35	8.44	0.283
9*.....	5.58	6.13	1.85	1.87	0.305	1.80	1.98	1.10	1.11	0.561	.....	.....	....	....	.....	17.15	18.83	7.86	7.94	0.422
10*.....	5.53	6.08	1.86	1.88	0.309	1.91	2.10	1.24	1.26	0.598	.....	.....	....	....	.....	30.30	33.30	6.55	6.62	0.199
11.....	3.55	3.90	1.57	1.59	0.408	1.15	1.26	0.54	0.60	0.495	89.6	98.4	60.6	61.3	0.623	35.75	39.30	14.28	14.43	0.367
12.....	6.04	6.60	0.46	0.47	0.070	1.53	1.67	1.00	1.01	0.605	.....	.....	....	....	.....	37.00	29.50	7.82	7.90	0.268

* In these cases the spinal fluid was apparently normal so far as the cells, the Wassermann and the Lange tests and the protein were concerned.

adequately controlled with known solutions and the recovery of added urea. The arginase error [9] associated with determinations of urea in whole blood are of no concern here.

DISTRIBUTION OF NONELECTROLYTES BETWEEN HUMAN PLASMA AND CEREBROSPINAL FLUID

In table 1 are presented typical results obtained from clinical material. In comparing these with similar figures of other investigators, it should be remembered that here the distribution was compared on the basis of the concentration of water in each fluid and accentuates the discrepancies in distribution found on a volume basis.

There is a definitely higher concentration of uric acid in the plasma than in the cerebrospinal fluid, an observation that has been made before. This is probably not due to the presence of nonuric acid substances in the plasma which react with the reagent, for Hubbard [10] found only a slight difference between the direct and indirect methods, and when the determinations were repeated in a number of cases with the indirect method, there was no appreciable change in relative results. The fact remains, however, that the determination of uric acid is not of such specificity or accuracy that any certain conclusions could be drawn from the difference in the distribution of this substance between the two fluids.

With one exception, the distribution of creatinine was such that the concentration of plasma was higher than that of the neural fluid. The distribution ratio bears no constant relation to that of either uric acid or urea. Since the substance or substances that are measured by this color reaction are unknown,[11] the only significance of the concentration in the cerebrospinal fluid is that the same reaction is given by this fluid and in higher degree by the plasma.

Dextrose, measured as a fermentable reducing substance, was notable in being present in the cerebrospinal fluid in much smaller concentration than in the plasma. Although this does not exactly agree with the recent observations which found the concentrations in the two fluids more nearly the same, most investigators determined not only dextrose but the total reducing substances, and Kubie and Shultz [12] found no close dependence of even this figure for the cerebrospinal fluid on that of the blood. Fremont-Smith [13] gave only from 1 to 15 per cent of the total

9. Addis, T.: Proc. Soc. Exper. Biol. & Med. **25**:365, 1928.

10. Hubbard, R. S.: Clifton M. Bull. **13**:88 (Sept.) 1927.

11. Behre, J., and Benedict, S.: J. Biol. Chem. **52**:11, 1922.

12. Kubie, L. S., and Shultz, G. M.: J. Exper. Med. **42**:565 (Oct.) 1925.

13. Fremont-Smith, F., and Dailey, M. E.: Cerebrospinal Fluid Chlorides, Arch. Neurol. & Psychiat. **14**:565 (Oct.) 1925.

reducing substances as the nondextrose fraction of the spinal fluid. This was the difference before and after hydrolysis, and it is difficult to see just how this method can give the concentration of the total reducing substances, which is dextrose. Removal by yeast is the only method by which dextrose may be definitely separated from other reducing substances. In any case, the distribution ratio of dextrose has little significance in this discussion because of the probability that the dextrose in the cerebrospinal fluid is utilized more rapidly by the cells which it bathes than it is restored from the blood.

The distribution of urea between the blood and the cerebrospinal fluid is both the most interesting and the most significant of the nonelectrolytes present in the blood and fluid. In every case a gross inequality in distribution of urea between the water of the two fluids was obvious. The accuracy and specificity of the determination of urea is probably greater than for the determination of any other nonelectrolyte. There is no reason to believe that it is either consumed or produced by any part of the nervous system or adjoining tissues. Since it is readily soluble and diffusible, the cerebrospinal fluid with a higher water content than plasma would be expected to have a higher concentration of urea if the distribution were equal. Not only was this not the case, but the water in the cerebrospinal fluid consistently maintained less urea than that of the plasma. Although one investigator, using modern methods,[14] reported an equal distribution of urea between the two fluids, others [15] agree that the plasma contains a higher concentration. That they failed to find a greater discrepancy is undoubtedly due to their failure to take into consideration the difference in water content of the two fluids. I have assumed, of course, as have others dealing with the distribution of electrolytes between body fluids,[16] that all of the water in the plasma and cerebrospinal fluid is free to dissolve urea and other substances, for there is no evidence [17] that water, which may be bound by the hydration of ions, or of more importance, by the imbibition of protein does not carry the same concentration of salts and other substances as the so-called free water with which it is associated. Should one assume that there is such bound water which is not available for the solution of urea, the distribution of this substance

14. Cullen, G. E., and Ellis, A. W. M.: J. Biol. Chem. **20**:511, 1915.

15. Myers, V. C., and Fine, M. S.: J. Biol. Chem. **37**:239, 1919. Egerer, G., and Nixon, C. E.: Comparative Studies in the Chemistry of the Blood and Spinal Fluid, Arch. Int. Med. **28**:561 (Nov.) 1921. Richon, L.; Vigneul, M., and Girard, J.: Compt. rend. Soc. de biol. **100**:747 (March 15) 1929.

16. Van Slyke, D. D.; Wu, H., and McLean, F. C.: J. Biol. Chem. **56**:765, 1923.

17. Neuhausen, B. S.: J. Biol. Chem. **51**:435, 1922.

would be even less understandable on a basis of pressure filtration or dialysis, for the greater concentration of protein in the serum would reduce the amount of water in which its urea is dissolved without causing a significant change in the concentration of the cerebrospinal fluid.

DISTRIBUTION OF UREA BETWEEN THE PLASMA AND CEREBROSPINAL FLUID OF NORMAL CATS

The reasons that make urea the most suitable of the nonelectrolytes to be examined for the purpose of this study have been enumerated. Even with such a satisfactory substance to work with, observations on man leave much to be desired. The use of strictly normal material is impracticable, and in any case it is hardly possible to manipulate the experimental conditions as desired. Observations were accordingly extended to normal cats and cats that had undergone certain experi-

TABLE 2.—*Distribution of Urea Between the Plasma and Cerebrospinal Fluid of Normal Cats*

	Plasma			Cerebrospinal Fluid			Ratio:
No.	Mg. of Urea per 100 Gm.	Gm. of Water per 100 Gm.	Mg. of Urea per 100 Gm. of Water	Mg. of Urea per 100 Gm.	Gm. of Water per 100 Gm.	Mg. of Urea per 100 Gm. of Water	Cerebrospinal Fluid / Plasma
1	102.70	91.70	112.10	63.00	98.70	63.80	0.569
2	47.29	92.30	51.20	30.05	98.70	30.46	0.595
3	44.45	92.20	48.20	42.22	99.00	42.70	0.886
4	45.38	92.39	49.14	32.85	98.90	33.21	0.676
5	51.65	91.70	56.50	29.20	98.90	29.53	0.523
6	46.10	90.00	51.47	28.20	98.40	26.68	0.557

mental procedures. The experiments were limited to determinations of urea, because of the greater significance of results obtained with this substance.

In table 2 are given the distribution ratios of urea between the plasma and cerebrospinal fluid of a number of normal cats. These were obtained under carefully controlled conditions by the methods that have been described. They bear out the results obtained from a study of the clinical material in man. In every case urea was unevenly distributed, and in one instance the water in the cerebrospinal fluid contained a concentration only half that of the water in the plasma.

EFFECT OF EXPERIMENTAL UREMIA ON THE DISTRIBUTION OF UREA

It seemed that additional evidence might be gained for one of the views in question by observing how closely the concentration of urea in the spinal fluid paralleled that of the plasma when uremia was produced experimentally by terminating the function of both kidneys.

In table 3 is shown the effect on the distribution of urea of an accumulation of urea in the blood. The concentration of urea in the cerebrospinal fluid increased at approximately the same rate, the average discrepancy in distribution remaining about the same. This result lends weight to neither of the hypotheses considered here, for similar increases in the concentration of urea in secretions, such as bile and milk,[18] and pressure filtration dialysates, such as ascitic fluid,[19] take place when urea accumulates in the blood.[20]

IN VITRO DIALYSIS OF PLASMA AGAINST CEREBROSPINAL FLUID

It has been stated that there is no reason to believe that any inequality in the distribution of a nonelectrolyte, such as urea, should exist between the plasma and the cerebrospinal fluid if the latter is a filtration dialysate, except incident to the difference in the water content of the two fluids.

TABLE 3.—*The Effect of an Experimental Uremia on the Distribution of Urea Between the Plasma and Cerebrospinal Fluid of the Cat*

	Plasma			Cerebrospinal Fluid			Ratio:
No.	Mg. of Urea per 100 Gm.	Gm. of Water per 100 Gm.	Mg. of Urea per 100 Gm. of Water	Mg. of Urea per 100 Gm.	Gm. of Water per 100 Gm.	Mg. of Urea per 100 Gm. of Water	Cerebrospinal Fluid / Plasma
1 A*	102.70	91.70	112.10	63.00	98.70	63.80	0.569
1 B	300.00	93.80	319.90	202.00	98.60	204.90	0.640
2 A	44.45	92.20	48.20	42.22	99.00	42.70	0.886
2 B	288.00	90.00	312.00	154.50	98.90	156.30	0.505
3 A	51.65	91.70	56.50	29.20	98.90	29.53	0.523
3 B	258.20	91.20	283.00	150.70	99.00	152.30	0.538

* A represents the normal state and B, twenty-four hours after uremia was induced.

This is on the assumption that a similar distribution of urea exists between the plasma and a transudate and would exist between them if separated by an artificial semipermeable membrane. That this is the case seemed certain, but there is little evidence bearing directly on this point. The possibility of some force or condition, such as the combination of urea and protein, which might lead to an uneven distribution, as protein on one side of a semipermeable membrane does with electrolytes, made it seem desirable to test this question by experiment. Three specimens of plasma were dialyzed against simultaneously obtained samples of cerebrospinal fluid to determine whether or not the distribution ratios would remain the same after dialysis. The results are presented in table 4. In the absence of the equal

18. Marshall, E. K., Jr., and Davis, David M.: J. Biol. Chem. **18**:53, 1914. Watanake, C. K.: Unpublished experiments quoted by Addis, T.: J. Urol. **1**:263, 1917.

19. Addis, T.: Personal communication.

20. Stealy, C. L.: J. Lab. & Clin. Med. **14**:162, 1928-1929.

or greater capillary pressure of the organism, some water naturally was drawn into the plasma by the colloidal osmotic pressure of the protein, until the limit of distention of the collodion sac containing the plasma was reached. In the first two experiments, more urea passed out of the plasma than water was drawn into it, for equilibrium between the two fluids was apparently not reached, as the concentrations of urea were still different when the experiment ended. This is even more significant, for it was the cerebrospinal fluid which acquired the higher concentration of urea. The two fluids were separated by a membrane of collodion and were allowed to stand at 2 C. for some time. The third system very nearly attained an equilibrium while the others did not, because of the frequent agitation of both phases, that in the sac by glass beads, and the outer fluid by stirring. Northrup [20] recently

TABLE 4.—*The Effect of in Vitro Dialysis of Plasma Against Cerebrospinal Fluid on the Distribution of Urea Between These Fluids*

Experiment	Days	Mg. of Urea per 100 Gm. of Plasma	Gm. of Water per 100 Gm. of Plasma	Mg. of Urea per 100 Gm. of Water	Mg. of Urea per 100 Gm. of Cerebrospinal Fluid	Gm. of Water per 100 Gm. of Cerebrospinal Fluid	Mg. of Urea per 100 Gm. of Water
			Before Dialysis				
1	...	50.70	90.90	55.80	22.57	98.90	22.80
2	...	28.28	91.20	31.00	18.20	98.80	18.42
3	...	31.40	90.95	34.80	16.20	98.99	16.37
			After Dialysis				
1	1	31.70	91.50	34.65	39.30	98.40	39.95
2	5	20.20	94.35	21.41	26.63	96.15	27.70
3	1	23.40	92.10	25.42	24.70	97.95	25.20

noted the necessity for movement in dialyzed fluids if equilibrium is to be obtained within a reasonable length of time. Far from supporting the dialysate theory of the origin of spinal fluid, these experiments in vitro dialysis make it almost certain that the fluid is not formed entirely in this manner.

CONCLUSIONS

It must be admitted that there are certain inequalities in the distribution of electrolytes between the plasma and cerebrospinal fluid of such a nature as would compensate for the presence of protein in considerable amounts in one of the fluids, and which strongly suggest that the cerebrospinal fluid is in the nature of a dialysate. However, it has been shown here that certain nonelectrolytes, particularly urea, are likewise unequally distributed between the two fluids and in such a manner that it is difficult to conceive of the spinal fluid being formed entirely by plasma ultrafiltration. The equilibrium which exists among the electrolytes is not incompatible with the assumption that the spinal fluid is

a secretion. This equilibrium may be looked on solely as the mechanism for bringing the osmotic pressure of the cerebrospinal fluid to approximately that of the plasma, just as the bile, concerning which there is no argument that it is a secretion, has essentially the same osmotic pressure as the plasma, minus its protein content. It is not so much the purpose to present these observations on the unequal distribution of urea as evidence in favor of the secretion theory, as to oppose the idea that the spinal fluid is solely an ultrafiltrate.

SUMMARY

Dextrose, creatinine, uric acid and urea are unequally distributed between the water of the cerebrospinal fluid and that of the plasma in clinical material obtained from man. The concentrations in the neural fluid are from 50 to 80 per cent of those of the plasma. Urea is likewise present in dissimilar concentration in the cerebrospinal fluid and plasma of normal cats and cats in which uremia was produced experimentally. When plasma is dialyzed in vitro against cerebrospinal fluid from the same subject, this unequal distribution of urea is not obtained. These results are evidence against the view that the cerebrospinal fluid is produced solely by ultrafiltration of the plasma.

CORRECTION

The Syndrome of the Brachium Conjunctivum and the Tractus Spinothalamicus. Colin K. Russel, M.D., ARCH. NEUROL. AND PSYCHIAT. **25:** 1003 (May) 1931.

In the fourth line of the summary, on page 1009, the words homolateral and heterolateral were transposed; in other words, the second clause of the first sentence in the summary should read: "both cases show a definite combination of symptoms, namely, loss of pain and thermal sense on the heterolateral side and ataxia, atonia and asthenia on the homolateral side."

THE COMBINED ACTION OF SOME CONVULSANT AGENTS IN SMALL DOSES AND THE ACTION OF BROMIDES IN EXPERIMENTALLY INDUCED CONVULSIONS *

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The facility with which a number of substances, such as absinthe, cocaine, alcohol, acid fuchsin, picrotoxin, caffeine and many others, will produce convulsions is well known. Some of them are used in experiments on animals, while others, such as ergot and alcohol, give rise to convulsions in man. All these substances belong to the exogenous group of convulsant agents. It is probable that there are a considerable number of toxins of endogenous origin that may give rise to convulsions. Convulsions are one of the most striking symptoms in uremia and eclampsia. In these conditions they may be associated with a high concentration of nitrogen in the blood of the patient, but the actual convulsant agent is unknown. The problem in so-called "idiopathic" epilepsy is difficult. The term idiopathic is not a good one, since it indicates that the disease is its own pathologic process. Great efforts have been made, particularly in the last decade, to discover possible biochemical manifestations of a pathologic nature in epilepsy. These studies have until now disclosed one significant factor, the increase of lactic acid in the blood and in the cerebrospinal fluid. This increase is present not only during and immediately after the convulsions, but also in the intervals, as was shown by one of us [1] in a previous study. This increase in the concentration of lactic acid was observed as late as three weeks after the last preceding convulsion, and the opinion was expressed that it was not due to the accumulation of lactic acid caused by the severe muscular movements and the asphyxia.

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* From the Neuro-Surgical Laboratory and the Department of Neurology of Columbia University.

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1. Osnato, M.; Killian, J. A.; Garcia, T., and Mattice, M. R.: Comparative Chemical Studies of the Blood and Spinal Fluid in Epilepsy, Brain **50**:581, 1927.

The increased concentration of lactic acid was found uniformly in all of the cases studied. The question arose: Has lactic acid any direct significance in the production of convulsive seizures? We, therefore, proceeded to inject lactic acid intravenously into cats under experimental conditions in order to study its effect. The technic of this procedure has been given elsewhere.[2]

We have done this in a number of animals, using various concentrations in order to get the effect of varying doses. We have used it also in combination with absinthe in cats and with acid fuchsin in frogs. The number of experiments, extending over almost two and one-half years, is too large to give in detail, and we have therefore tabulated the results. We have also tried the effects of feeding bromides to cats for some time previous to the injection of absinthe, and the effects of intravenous injections of large doses of sodium bromide (up to 2.5 Gm.) a few hours before the administration of the absinthe, in

TABLE 1.—*Intravenous Injections of Lactic Acid into Cats*

Dose per Pound of Body Weight, Gm.	Effects
0.1	Severe convulsions, pneumatorrhexia, salivation, twitching, death
0.09	Clonic followed by tonic convulsions, death
0.08 to 0.087	Severe convulsions, becoming tonic; respiratory distress, death
0.07 to 0.076	Dilation of pupils, clonic and tonic convulsions, respiratory distress, death
0.06	Respiratory distress, twitching of muscles and eyes
0.05 to 0.057	Dilation of pupils, clonic and tonic convulsions, respiratory difficulty, slight generalized twitchings, occasionally death
0.04	Slight twitching, respiratory difficulty
0.035	Dilation of pupils, excitement, struggles
0.02	Dilation of pupils, excitement, perspiration on paws

order to determine its effect on the dosage of absinthe necessary to elicit convulsions.

Table 1 represents the results obtained with injections of lactic acid. Concentrations of lactic acid as high as 0.1 Gm. per pound of body weight produced severe convulsions, followed by death. The same effect has been observed with smaller doses, such as 0.076 Gm. per pound of body weight. Along with the motor manifestations there were other signs, such as respiratory difficulty, gasping for air, perspiration of the paws, cries, dilated pupils, etc. With doses of 0.07 Gm., or less, per pound of body weight, the motor manifestations became less severe, with twitchings occurring in the different groups of muscles. On the other hand, respiratory distress was marked, and other signs of autonomic involvement were present. Occasionally clonic and tonic movements were still observed with a dose of 0.05 Gm. per pound of

2. Pike, F. H.; Elsberg, C. A.; McCulloch, W. S., and Rizzolo, A.: Some Observations on Experimentally Produced Convulsions, Am. J. Psychiat. **9**:261, 1929.

body weight, but in all probability this was an exceptional instance. On another occasion the same dose gave the usual respiratory and autonomic manifestations in addition to a few slight generalized twitchings of the skeletal muscles.

The lowest dose that gave motor manifestations in the form of twitchings was 0.04 Gm. per pound of body weight. Below that dose, only respiratory and autonomic signs were observed, and the cats usually did not succumb from the injection of lactic acid.

Table 2 represents the results of the administration of lactic acid combined with absinthe. These experiments may be divided into two groups: In group 1, a subconvulsant dose of absinthe was injected

TABLE 2.—*Combined Effects of Intravenous Injections of Absinthe and Lactic Acid*

Dose of Absinthe, Cc. per Pound of Body Weight	Dose of Lactic Acid, Gm. per Pound of Body Weight	Effect
0.03	0.06, 30 minutes later	Immediate but transient convulsion
	0.1, 7 minutes later	Tonic convulsion, death
0.035	0.03, 46 minutes later	Transient clonic convulsion, respiratory distress
0.03	0.06, 20 minutes later	Twitchings
0.03	0.023, 2 minutes later	Severe convulsion
	0.056, 8 minutes later	Convulsion, death
0.045	0.05, 15 minutes later	Severe convulsion, death
0.045	0.05, 10 minutes later	Convulsion
	0.05, 10 minutes later	Convulsion, death

TABLE 3.—*Combined Effect of Intravenous Injection of Lactic Acid and Absinthe*

Dose of Lactic Acid, Gm. per Pound of Body Weight	Dose of Absinthe, Cc. per Pound of Body Weight	Effect
0.025	0.02, 2 minutes later	Severe convulsion
0.03	0.02, immediately	Twitchings
0.06	0.015, immediately	Clonic and tonic convulsions, death
0.06	0.025, immediately	Tonic convulsions, death

intravenously and was followed by the injection of a subconvulsant dose of lactic acid. From the table it will be seen that, with very few exceptions, there were immediate convulsions followed by the death of the animal. In other words, a dose of lactic acid which, when used alone, will produce only respiratory signs or twitchings, when used with a subconvulsant dose of absinthe will provoke severe, though not always lethal, convulsions. The combined action of the two agents, when each is given in subconvulsant doses, is greater than could be accounted for by the action of either one alone.

In group 2 (table 3) we first injected lactic acid in concentrations from minimal to convulsive, but still sublethal, doses, and followed them with subconvulsant doses of absinthe. In all instances there were clonic and tonic convulsions, but it is interesting to note that in the cases in which subconvulsant doses of lactic acid were given, the con-

vulsions were not lethal, whereas with a higher concentration of lactic acid alone death followed immediately after the convulsion.

Another group of experiments with lactic acid and acid fuchsin, used separately and combined, was done on frogs.

In agreement with Abel,[3] Barbour,[4] Joseph,[5] Meltzer[6] and Syz,[7] we found that no convulsions were produced when acid fuchsin was injected in small doses. Meltzer claimed to have obtained convulsions in frogs with 0.005 mg. per gram of the body weight. Thomas[8] was able to produce convulsions with much smaller doses when a small needle puncture of the anterior part of the brain had previously been made. Abel obtained the same results with small, nonconvulsant doses of acid fuchsin by removing the anterior third of the cerebral hemispheres of the frog.

Syz[9] showed that the same effect can be produced by immersing the frog under water or white oil, or by placing it in an atmosphere of nitrogen after the administration of a small dose of acid fuchsin ordinarily not sufficient to cause convulsions. A number of other factors, like fatigue (Barbour[4] and Abel[3]) and cardiectomy (Meltzer and Joseph[5]), seem to decrease the convulsant dose of acid fuchsin. With this in mind, and considering the results of experiments with lactic acid in cats, we decided to investigate the possible effect it might have in frogs. We must, however, mention here the claim of Froehlich and Sole,[10] who stated that lactic acid decreases the convulsive symp-

3. Abel, J. J.: On the Action of Drugs and the Function of the Anterior Lymph Hearts in Cardiectomized Frogs, J. Pharmacol. & Exper. Therap. **3**:581, 1912.

4. Barbour, H. G., and Abel, J. J.: Tetanic Convulsions in Frogs Produced by Acid Fuchsin, and Their Relation to the Problem of Inhibition in the Central Nervous System, J. Pharmacol. & Exper. Therap. **2**:167, 1910.

5. Joseph, D. R., and Meltzer, S. J.: On the Convulsant Action of Acid Fuchsin upon Frogs Deprived of Their Cardiac Circulation, J. Pharmacol. & Exper. Therap. **3**:183, 1911.

6. Meltzer, S. J.: The Distribution of Solutions in Cardiectomized Frogs, J. Exper. Med. **13**:542, 1911.

7. Syz, H. C.: On the Entrance of Convulsant Dyes into the Substance of the Brain and Spinal Cord After an Injury to These Structures, J. Pharmacol. & Exper. Therap. **21**:263, 1923.

8. Thomas, J. E.: Some Factors in the Production of Acid Fuchsin Convulsions in Frogs, J. Pharmacol. & Exper. Therap. **17**:334, 1921; Factors Affecting the Susceptibility of Frogs to the Convulsant Action of Acid Fuchsin, ibid. **23**:307, 1924.

9. Syz, H. C.: On the Influence of Asphyxia upon the Action of Convulsant Dyes and upon Their Entrance into the Substance of the Central Nervous System, J. Pharmacol. & Exper. Therap. **30**:1, 1926.

10. Froelich, A., and Sole, A.: Der Einfluss von Sauren und Alkalien auf die Wirkung einiger Krämpfgifte, Arch. exper. Path. u. Pharmacol. **104**:32, 1924.

toms following injections of strychnine, nitrate, thebaine, acetate and picrotoxin into warm and cool-blooded animals, whereas, alkali increases the potency of these convulsant agents. They also claimed that convulsions arising from strychnine fail when the supply of oxygen is reduced.[11] They did not mention the combination with acid fuchsin or with absinthe.

A clue to the mode of action of lactic acid is found in the experimental work of Matthews,[12] who concluded that lactic acid increases the permeability of small capillaries and of the cells themselves to substances that are soluble in water. The activity of lactic acid in producing respiratory and other symptoms, in addition to convulsions, is explained, according to Bayliss and Starling,[13] by the fact that the common factor in asphyxia is the increased p_H of the blood due to

TABLE 4.—*Separate and Combined Effects of Acid Fuchsin and Lactic Acid on Frogs*

Dose of Acid Fuchsin, Gm. per Gram of Body Weight	Dose of Lactic Acid, Gm. per Gram of Body Weight	Effect
0.005	.....	Immobility and recovery
0.0083	.....	Rigidity, tetanus, death
	0.001	Immobility and recovery
	0.003	Immobility and death
0.0018	0.0024	Clonic and tonic movements; generalized convulsions, death in 3 minutes
0.0041	0.0027	Immobility followed by recovery
	0.027 2 hours later	Severe convulsions, death
0.005	0.003	Immobility, severe clonic and tonic convulsions in 16 minutes, death in 26 minutes
0.005	0.001	Clonic and tonic convulsions, death
0.006	0.004	Severe convulsions, death in 5 minutes
0.002	.....	Inactivity and recovery
0.003	0.004 1 hour later	Clonic and tonic convulsions, death in 30 minutes

lactic acid, and that this is associated with a discharge of epinephrine into the blood and the resultant splanchnic stimulation. (The latter, of course, accounts for the autonomic symptoms occurring during convulsions due to lactic acid.)

In our experiments (table 4), no convulsions were produced even when a relatively large dose of acid fuchsin (0.005 Gm.) was injected into the ventral lymph sac. Except, perhaps, for a temporary depression and general slowing down of the frog, nothing was observed.

11. See also Stewart, G. N.; Guthrie, C. C.; Burns, R. L., and Pike, F. H.: The Resuscitation of the Central Nervous System of Mammals, J. Exper. Med. **8**:309, 1906.

12. Matthews, A. P.: Physiological Chemistry, ed. 4, New York, William Wood & Company, 1925, p. 648.

13. Bayliss and Starling: The Nervous Control of the Blood Vessels, in Starling, E. H.: Principles of Human Physiology, ed. 2, London, J. & A. Churchill, 1915, p. 982.

Larger doses of about 0.0087 Gm. of acid fuchsin produced tetanus, clonic and tonic convulsions, and death shortly afterward.

Lactic acid, when used in small doses of 0.001 Gm. per gram of body weight, had no greater effect than to produce a temporary immobility with complete recovery. With doses even three times as large, 0.003 Gm., no convulsions were observed, but the frogs died about twenty-four hours or more after the injection.

The combination of lactic acid and acid fuchsin produced interesting results. A small dose of acid fuchsin was injected into a frog, and was followed by a small dose of lactic acid. All types of convulsions were observed, with subsequent death. Occasionally, however, the frog would recover, but an additional small dose of lactic acid, when injected even two hours later, had a lethal effect. Severe convulsions with tetanus were observed with larger doses of lactic acid and acid fuchsin, but even here the amount injected was under the subconvulsant dose of either one taken separately.

TABLE 5.—*Combined Effects of Lactic Acid Followed by Acid Fuchsin*

Dose of Lactic Acid, Gm. per Gram of Body Weight	Dose of Acid Fuchsin, Gm. per Gram of Body Weight	Effects
0.003	0.006	Clonic and tonic convulsions, rigidity, death
0.001	0.0062	Strong clonic and tonic convulsions
0.003	.....	Inactivity and recovery
0.003	.....	Inactivity and recovery
	0.0023 22 min. later	Inactivity and recovery

The injection of acid fuchsin about forty-five minutes after the injection of lactic acid (table 5), and conversely, gave results of interest. In the first type of experiment no convulsions were observed, possibly due to the fact that sufficient time elapsed between the injection of lactic acid and acid fuchsin to allow the former to be metabolized. When, however, acid fuchsin was used first and lactic acid added an hour later, severe lethal convulsions appeared, although they were somewhat delayed. The usual convulsive effects were observed when the injection of acid fuchsin followed the injection of lactic acid within two or three minutes.

We have been unable to produce convulsions in frogs from the administration of absinthe, either alone or in combination with subconvulsant doses of lactic acid or acid fuchsin, even when injected intravenously. We do not know the reason for this failure.

ANTICONVULSANT DRUGS

The number of known anticonvulsant agents is limited. A few of them have found wide use in the treatment of convulsive disorders. Among them, bromide is the oldest; phenobarbital has been used in

the last fifteen years.[14] More recently, borates have been found to have antispasmodic properties. Their first use was due to Gowers.[15] In animal experimentation, bromide is said to have been used by Albertoni in 1879, and by Rovighi and Santini at about the same time. Albertoni is quoted by Luciani as having shown that if potassium bromide is administered to dogs for several days in succession, the electrical excitability of the cortex is so much reduced that even strong currents fail to produce an epileptic attack. This author is said by Luciani to have shown also that when successive or lethal doses of quinine are injected into dogs previously treated with bromide, convulsions are not evoked. When atropine is administered, the convulsions following injections of quinine are severe. The reference quoted by Luciani [16] was read in the original by one of us, and nothing

TABLE 6.—*Effect of Intravenous Injection of Sodium Bromide on Response to Absinthe*

Bromide, Gm. per Pound of Body Weight	Absinthe, Cc. per Pound of Body Weight	Effects
0.14	0.021	Twitches
	0.028	Twitches
	0.035	Twitches, cries
0.25	0.02	No reaction
	0.03	Twitchings, cries
	0.035	Twitchings, nystagmus
	0.04	Clonic convulsion
	0.05	Tonic extension, death
0.3	0.02	Transient excitement
	0.025	Transient excitement
	0.03	Rapid respiration, cries
	0.035	Cries, twitches
	0.04	Rapid respiration, tonic extension, death
0.38	0.04	Tonic extension, few clonic twitches, death

was found in Albertoni's work concerning experiments with potassium bromide in any of the animals experimented on, or of its alleged effects on experimentally produced convulsions. Albertoni also did not report any experiments he himself made with quinine. This reference is probably a mistake, for this work seems to have been done by Rovighi and Santini.

Rovighi and Santini [17] found that bromides reduced or abolished the convulsions arising from the injections of picrotoxin, while atropine increased them.

14. Notkin, J.: Chloride-Bromide Treatment in Epilepsy, Arch. Neurol. & Psychiat. **21**:165 (Jan.) 1929; Basal Metabolic Rate in Untreated and Treated Patients with Epilepsy, ibid. **24**:1231 (Dec.) 1930.

15. Gowers, in Crouzon, O.: Le syndrome épilepsie, Paris, Gaston Doin, 1929, p. 228.

16. Luciani: Annali universale di medicina e chirurgia, 1879, vol. 249.

17. Rovighi and Santini: Sur les convulsions épileptiques par les poisons, Arch. ital. de biol. **2**:278, 1882.

Our investigation along these lines consisted of two types of experiments: In one (table 6) cats were given intravenous injections of various concentrations of sodium bromide followed by injections of absinthe about three or four hours later. These reactions were identical with those observed when absinthe alone is used. The intravenous injection of bromide did not abolish the effect of absinthe. Our general impression is that the lethal dose of absinthe may be somewhat smaller after the injection of bromide. Subconvulsant doses of absinthe caused the usual respiratory manifestations.

The second group of experiments consisted of feeding a number of cats with a mixture of sodium bromide, sodium chloride, proteins, fats and spices. This mixture was given to the cats with their food daily, each one receiving a definite daily amount of bromide.

TABLE 7.—*Effect of Feeding Bromide on Response to Absinthe*

Daily Total Dose of Bromide, Gm.	Days Fed	Absinthe, Cc. per Pound of Body Weight	Effects
0.55	21	0.028	No reaction
		0.033	Few twitches
		0.040	Twitches
		0.046	Some tonic effect but no real convulsion, death
1.1	7	0.020	Rapid respiration
		0.025	Slight twitches
		0.030	Tonic extension, cries, death
1.1	15	0.020	Excitement, cries
		0.036	Twitches
		0.040	Tonic extension, death
1.1	21	0.036	No effect
		0.036	No effect
		0.040	Dilated pupils, occasional twitch
		0.045	Dilated pupils, twitch
		0.050	Cry, tonic convulsion, respiratory gasps, death

We fed one cat with 0.55 Gm. of bromide daily for twenty-one days, and three cats with 1.1 Gm. of bromide daily for seven, fifteen and twenty-one days, respectively.

The first cat (table 7) showed a decreased reaction to absinthe as the dose of 0.046 Gm. of absinthe per pound gave really little convulsant effect, although it was lethal. In the other cats fed seven days or longer with 1.1 Gm. of bromide daily, we had practically the same results. Low doses of absinthe had hardly any effect; doses that usually cause severe convulsions produced only slight convulsive manifestations in our cats.

We believe, therefore, that only a more or less prolonged administration of bromide may affect the convulsant action of absinthe.

SUMMARY AND CONCLUSIONS

These experimental studies were made chiefly because of the discovery of an increased concentration of lactic acid in the blood and

cerebrospinal fluid in epileptic persons. The experiments with lactic acid alone in concentrations of 0.1 Gm. per pound of body weight produced severe lethal convulsions in cats, accompanied by great respiratory difficulty and sympathetic disturbances of various kinds. Occasionally, clonic and tonic movements were obtained with doses of 0.05 Gm., rarely with smaller doses.

The work suggests that lactic acid by itself is not a satisfactory convulsant chemical agent. The convulsions are too apt to be followed by death.

In a second group of studies (table 3), lactic acid was injected in minimal, sublethal convulsant doses followed by subconvulsant doses of absinthe. In every instance typical clonic and tonic convulsions ensued without death. It is obvious that lactic acid enhanced the convulsant effect of absinthe: probably the mechanism is due to the fact that lactic acid has the effect of increasing the permeability of the blood vessels, and perhaps of the cells themselves, to water-soluble substances.

Similar experiments on frogs with acid fuchsin make it possible to draw similar conclusions.

Experiments in which cats were fed for long periods with a sodium bromide preparation showed a decreased convulsant reaction to absinthe, but the lethal effects of ordinarily sublethal doses of absinthe were increased. Cats fed for brief periods with this preparation of sodium bromide reacted promptly with convulsions to convulsant doses of absinthe.

Only a fairly prolonged administration of bromide diminishes the convulsant action of absinthe in cats.

Clinical Notes

CHANGES IN THE MOTOR NERVE CELLS IN POLIOMYELITIS *

C. Helen Craw, M.D., Toronto, Canada

Although poliomyelitis (infantile paralysis) is a general systemic disease, the virus attacks the motor cells of the anterior horns of the spinal cord in a specific manner. As a rule these nerve cells suffer damage out of all proportion to any other cells in the body. This remarkable specificity has never been satisfactorily explained. The suggestion that the changes in the anterior horn cells are secondary to thrombosis of the anterior spinal artery (Batten, 1902) has been discredited, but it is not yet generally accepted that the change is a direct effect of the virus or its toxin, and is not secondary to the inflammatory reaction in the vessels and supporting tissue of the cord.

From a study of fifteen cases, Blanton [1] (1917) stated that the anterior horn cells suffer from the onset of the disease in the cord. He concluded that the mechanical factors of edema, congestion, compression and invasion of the tissue by wandering cells were not primary, and that hemorrhage was not the serious factor advanced by some investigators. Abramson [2] came to similar conclusions. He noted that in some sections the destruction of the nerve cells was out of all proportion to the degree of cellular infiltration.

Howe,[3] in describing the pathologic process in a number of cords of human beings and monkeys infected with poliomyelitis, claimed that there were eight different types of changes in the nerve cells, and that these changes were so diverse in character that they could not represent different phases of the same destructive process. His eight varieties show different combinations of cloudy swelling, chromatolysis and vacuolization and various degrees of neuronophagia. He believed that the changes in the nerve cells ("ectodermic") were not secondary to the inflammatory infiltration ("mesodermic change"), but represented the specific action of the virus. He described an epidemic of paralysis in cats, which he believed to be poliomyelitis. In these cords there was ectodermic reaction only. It has since been claimed that only man and the monkey are susceptible to the virus of poliomyelitis, but monkeys' cords have been observed in which the changes in the nerve cells are severe in the absence of interstitial (mesodermic) reaction.

Hassin [4] contrasted the pathologic process in an acute case of poliomyelitis with that in one of epidemic encephalitis. He observed in the anterior horn of

* Submitted for publication, Oct. 16, 1930.

* From the Department of Anatomy, University of Toronto, and the Hospital for Sick Children, Toronto.

1. Blanton, W. B.: Anatomical Study of Poliomyelitis, J. M. Research **36**:1 (March) 1917.

2. Abramson, H. L.: Acute Poliomyelitis, Arch. Int. Med. **22**:312 (Sept.) 1918.

3. Howe, H. S.: Pathology of Poliomyelitis, J. Nerv. & Ment. Dis. **48**:97 (Aug.) 1918; **48**:206 (Sept.) 1918, and **50**:409 (Nov.) 1919.

4. Hassin, G. B.: Comparative Histopathology of Acute Anterior Poliomyelitis and Epidemic Encephalitis, Arch. Neurol. & Psychiat. **11**:28 (Jan.) 1924.

the poliomyelitic cord swollen ganglion cells with pale dislocated nuclei and others "liquefied" with no trace of Nissl granules. He found distinct neuronophagic phenomena to be rare. In contrasting the two diseases he noted that the changes in the nerve cells were more marked in poliomyelitis and were confined to the anterior horn, while the cells of the anterior and posterior horns of the encephalitic cord were equally involved.

Hurst [5] made a careful study of the pathologic changes in experimental poliomyelitis. He showed conclusively that in the cords of monkeys the changes in the nerve cells are primary, but are usually accompanied by inflammatory change in the interstitial tissue. His observations will be discussed in detail later.

PERSONAL OBSERVATIONS

An opportunity recently occurred for studying the medulla and cord in a patient with acute poliomyelitis.

REPORT OF CASE

History.—A child, aged 4 years, was observed by her parents one evening to be breathing faster than usual. Her health had previously been good. She did not complain of discomfort, and slept well. The next day, a painless paralysis progressively involved the muscles of the neck, arms and back. The lower limbs were apparently uninvolved. She lost her voice, became cyanotic and died within thirty hours of the first sign of the disease.

The diagnosis of poliomyelitis was made, and at autopsy the medulla and spinal cord were removed and fixed in 10 per cent formaldehyde and saline solution preliminary to a detailed investigation of the changes in the nerve cells.

Technic.—Blocks of the cervical, thoracic and lumbar cords and of the medulla were embedded in paraffin, cut at from 7 to 10 microns and stained with Nissl and other stains. Cresyl violet was found to be much more satisfactory than methylene blue (methylthionine chloride, U.S.P.) or toluidine blue, as it is as effective in staining the Nissl granules in a uniform manner, and is much more permanent. Sections were stained overnight in a solution of 10 drops of concentrated cresyl violet to 50 cc. of distilled water. After decolorization in 95 per cent alcohol the sections were cleared in oil of cajuput and xylol. Many sections cut in the horizontal and in the longitudinal planes of the cord were mounted in series. Serial sections give a much more complete picture, as one is able to study the same cell in several sections.

HISTOLOGIC STUDIES

General Pathology.—In the cervical and thoracic segments of the cord a diffuse infiltration of inflammatory cells into the anterior horns was seen with a striking absence of motor cells. The nerve cells at the base of the posterior horns were affected to a comparatively slight degree. The lumbar cord showed a more patchy interstitial infiltration, more dense in the mesial halves of the anterior horns. In these areas nerve cells were absent, but more laterally many large and apparently normal cells were seen, while a minority showed various stages of degeneration. The interstitial infiltration throughout the length of the cord was fairly sharply limited to the gray horns, although there were occasional foci of cells in the white matter, especially in the anterior columns.

5. Hurst, E. W.: Histology of Experimental Poliomyelitis, J. Path. & Bact. **32**:457 (July) 1929.

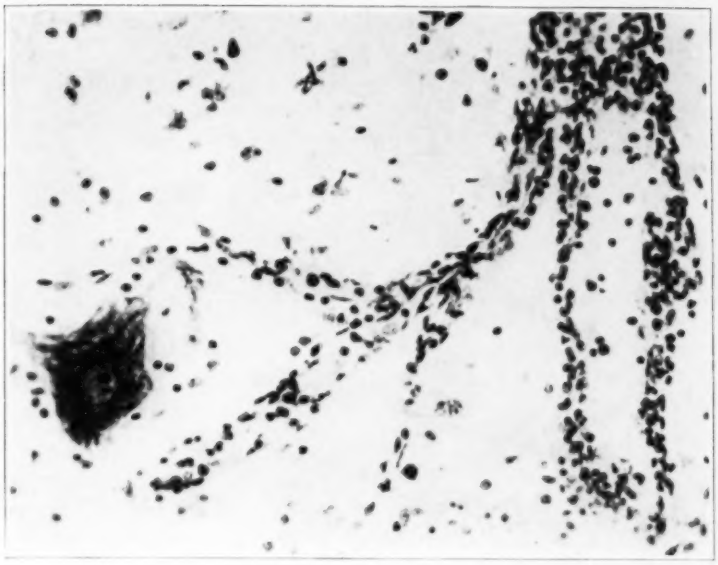


Fig. 1.—A vessel in the anterior horn of a lumbar segment of the cord. Perivascular infiltration is well marked, and the nerve cell shows early chromatolysis.

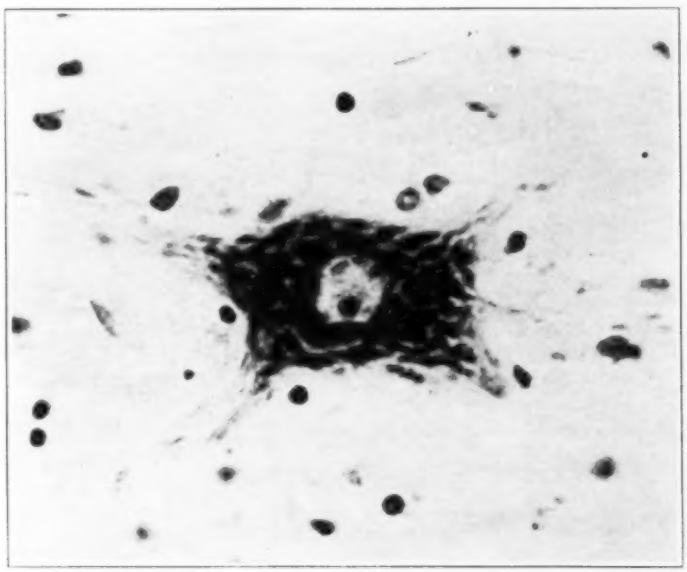


Fig. 2.—An anterior horn cell from the normal cord of a child aged 3 years.

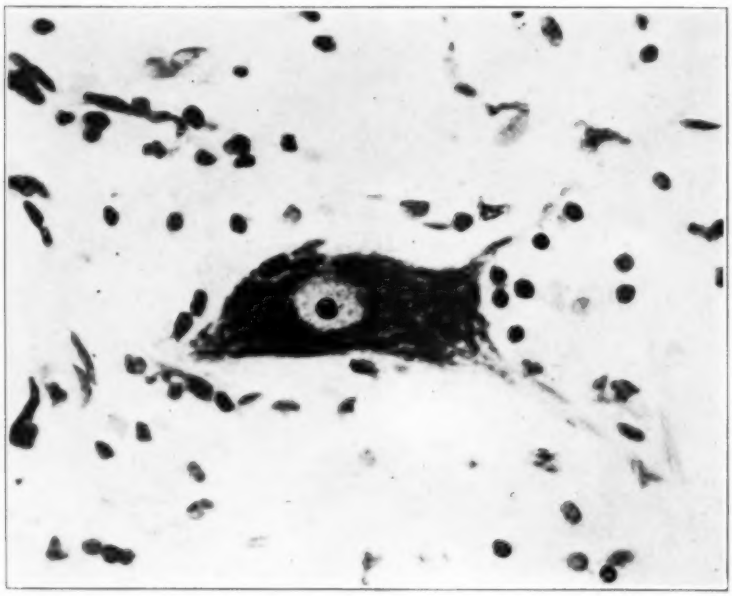


Fig. 3.—An anterior horn cell from the lumbar region of the infected cord, showing the earliest stage of degeneration as evidenced by less distinctly outlined Nissl granules.

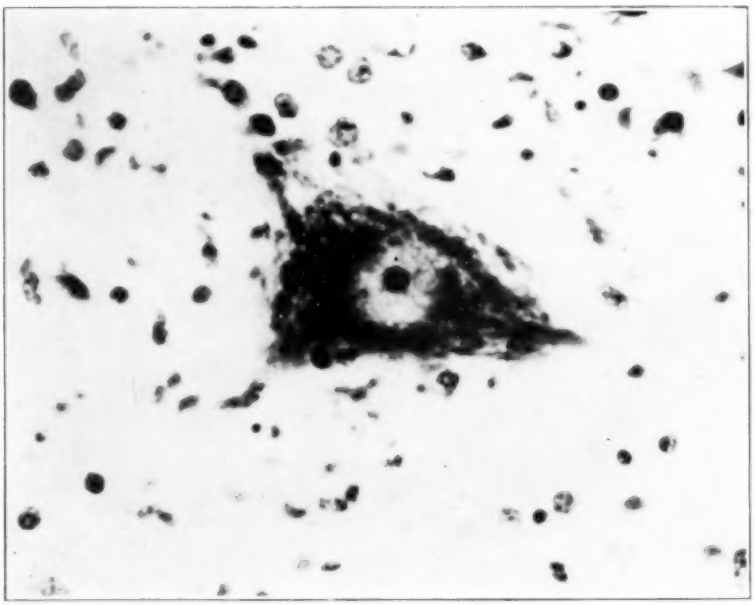


Fig. 4.—A cell showing swelling and irregular clumping of stainable substance.

In the gray and white matter alike, the blood vessels showed a marked perivascular infiltration of small round cells (fig. 1). A similar infiltration was seen in the meninges in all regions of the cord, but to a most marked degree in the lumbar region, which was the part of the cord showing the least destruction of the nerve cells. Hemorrhage was rarely found, although sought with care in sections stained with hematoxylin and eosin and with Mallory's connective tissue stain. There was little evidence of edema.

Changes in the Motor Nerve Cells.—I studied in detail the specific effect of the virus of poliomyelitis on the anterior horn cells of the spinal cord. The earliest changes in the nerve cells were observed in the lumbar region of the cord and are illustrated in figures 3 to 7, which are photographs of cells in various stages of degeneration, and can be compared with the photograph (fig. 2) of a motor cell from a normal cord, which was fixed and stained in exactly the same manner. In general the severity of the lesions in the cells varied directly with the degree of interstitial infiltration in its immediate vicinity, but there were exceptions to this rule. Apparently normal cells were seen lying in an area of infiltration; on the other hand, degenerating cells in an uninfiltrated area were rarely found. Close observation of certain cells, which were at first regarded as absolutely normal, revealed the fact that the Nissl granules had lost the distinctness of outline seen in normal cells. This was often true only of the granules of a small portion of the cell, usually those situated centrally, while the rest of the cell showed Nissl bodies distinctly outlined. The ground substance stained more deeply and was blurred in areas in which the Nissl bodies were replaced by finer and less distinct particles. Such an area is seen to the right of the nucleus in the cell in figure 3, while a more general "powdering" involves almost all the stainable (Nissl) substance of the cell in figure 1. In these cells the nucleus was usually clearly differentiated, centrally placed and contained a large, round, deep purple nucleolus. Occasionally the nucleus stained more deeply than normal. The outline of the cell body was normal.

In the next stage (figure 4) the stainable substance was irregularly clumped, giving a picture of large masses of stainable substance among diffuse powdery material. Parts of the cell often did not take the stain at all. The cell body generally appeared swollen. The nucleus was often normal, but at times it was less clearly outlined and occasionally was eccentrically placed, as in the cell in figure 5. This cell shows the diffuse powdering and clumping of the stainable substance in the cell body, while the rod-shaped Nissl granules of the dendritic processes are normal.

Phagocytosis of these degenerating cells was not so marked in this cord as is frequently described in poliomyelitis; nevertheless, there were many nerve cells (figs. 5 and 6) that showed small phagocytes of different types along their borders, often lying in small indentations of the cell margin. Some of these cells were polymorphonuclear leukocytes, others were lymphocytes, and still others were peculiar rod-shaped cells, often named polyblasts, and believed by Hurst to be microglia. This process of neuronophagia must be concerned with the removal of cells as they become destroyed by the virus. However, some cells which still contained considerable stainable substance were attacked by the phagocytes, while others had evidently reached a further stage in degeneration before they were removed. The latter had a cytoplasm of a light-staining foamy appearance (fig. 6), containing few or no coarse particles of stainable substance. The nucleus was less distinctly defined and more deeply stained, and the nucleolus was usually round, occasionally distorted in outline and sometimes larger than normal.

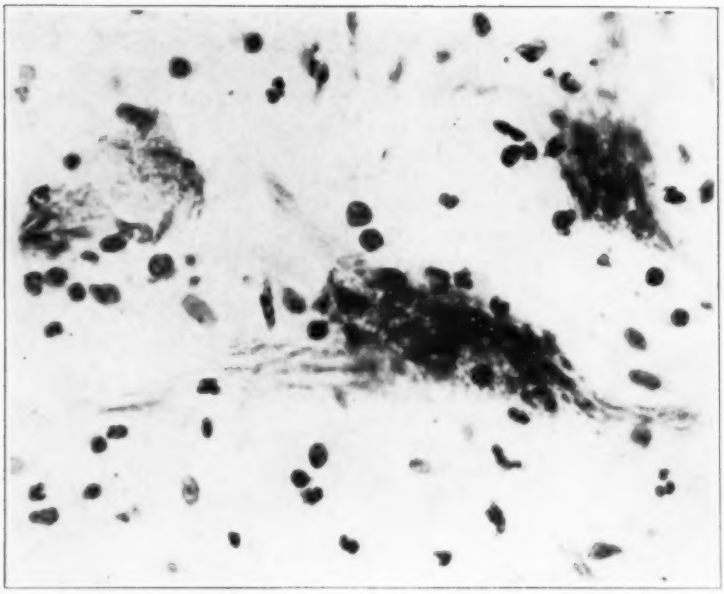


Fig. 5.—Similar cell with nucleus displaced to its lower margin and showing early neuronophagia. Lumbar cord of a patient with poliomyelitis.

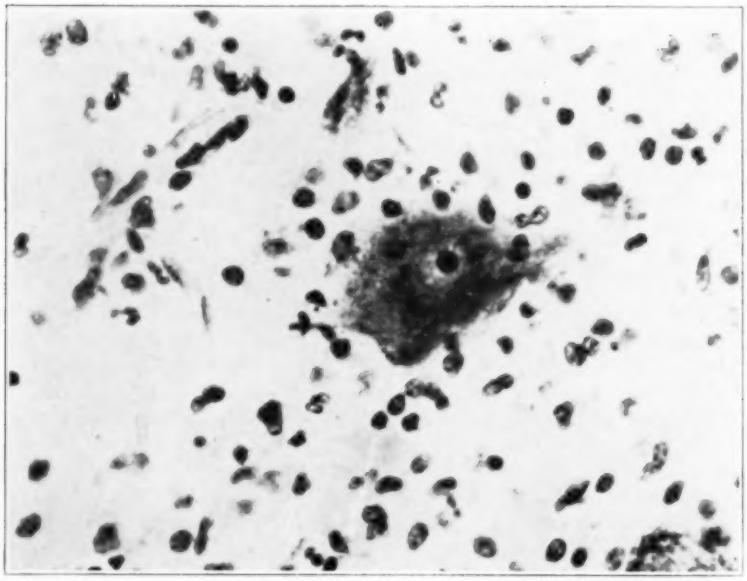


Fig. 6.—Cell severely damaged and partially removed by phagocytes in the lumbar cord of a patient with poliomyelitis.

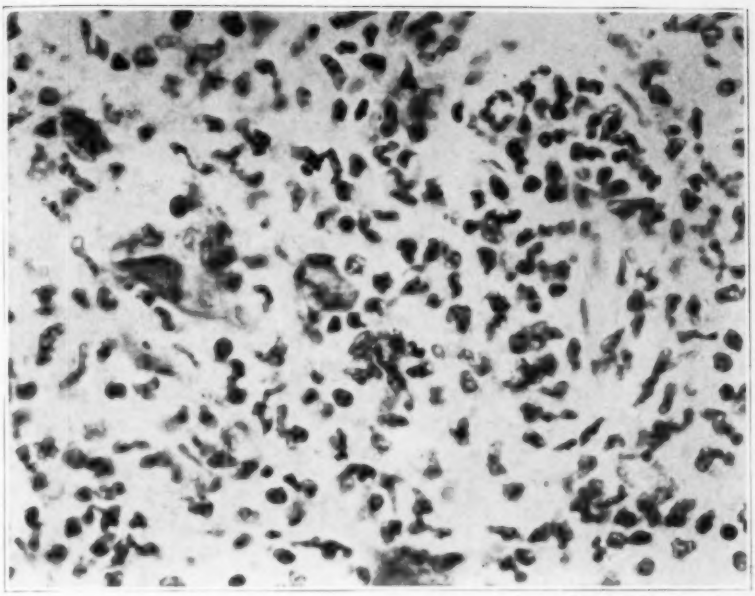


Fig. 7.—Fragments of motor cells in an area of interstitial inflammatory tissue in the lumbar cord in a patient with poliomyelitis.

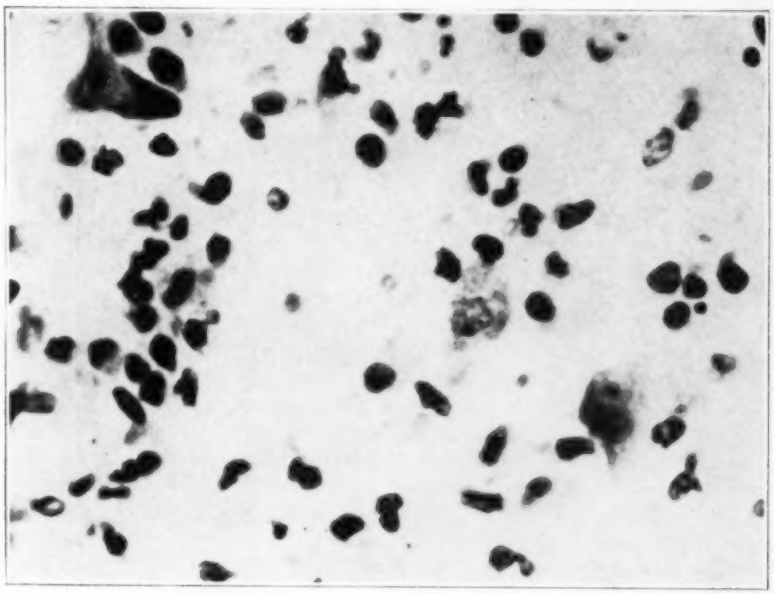


Fig. 8.—Similar cell fragments in the cervical region of the cord in a patient with poliomyelitis. A collection of fourteen cells toward the left of the photograph shows the last stage of neuronophagia.

Finally, mere fragments of cells were seen in the most densely infiltrated parts of the anterior horn (fig. 7). A fragment often contained a small indefinite nucleus with a small distorted nucleolus. Similar remains of cells were found in the cervical region (fig. 8). In this photograph a group of inflammatory cells, about fifteen in number, is seen massed together against a faintly staining background, evidently representing the end-stage of neuronophagia.

One can, therefore, follow a cell through the phases of swelling and chromatolysis, with or without eccentration of the nucleus, to its final solution and removal by phagocytes. I believe that this is the general process of destruction of motor cells in poliomyelitis.

On the other hand, figure 9 represents the type of cell found only by careful search in the thoracic and cervical regions of this cord, where almost all the

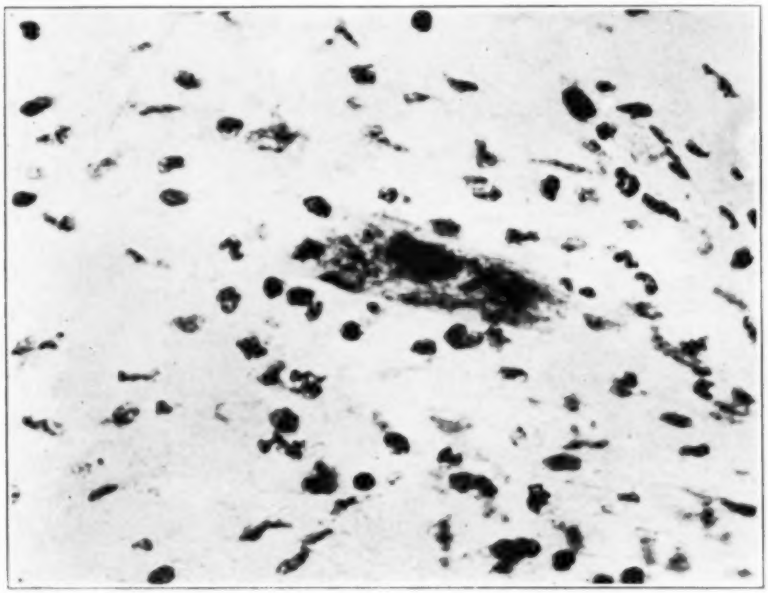


Fig. 9.—A cell from the anterior horn of the thoracic region of the cord. Note the serious degeneration of the second type described in the text.

anterior horn cells were destroyed. The outline of the cell body was comparatively unaltered. There was no evidence of swelling; in fact, these cells were so small as to suggest cell shrinkage. Considerable stainable substance was present, although it was irregularly granular and clumped. Most striking was the deep-staining nucleus with distorted margin. Less commonly the nucleus was light-staining and contained a small granular nucleolus. There was evidence of a certain amount of neuronophagia of cells undergoing this type of change. I did not observe the vacuolization described by others as a common process, but occasionally a cell showed a small clear area at its margin or situated more deeply in the cell body, often containing a phagocytic cell. A very small clear area is seen on the inferior margin of the cell photographed (fig. 9). The appearance of shrinkage and that of vacuolization can easily occur as artefacts, but I was struck by their rarity in the examination of this cord.

Hurst described two types of cellular destruction. The first type of destruction is that which progresses rapidly but through a sequence of changes, yielding finally a cytoplasm that stains deeply in parts and feebly in others, with reticulation and the appearance of vacuoles. The second type of destruction he observed after the injection of a virulent strain of virus, and he described it as a nerve cell little altered in outline, but with fading nucleus and showing at first little tendency to neuronophagia. I believe that the latter type of cell—"obviously killed almost instantaneously"—is similar to the cells found in the parts of this cord that were most seriously attacked by the disease and were swept almost clean of motor cells.

In conclusion a few words may be said about the changes in the cells in other parts of the cord and in the medulla. It is most remarkable that in many sections of the thoracic cord every anterior horn cell was destroyed, but the large cells of the dorsal nucleus (Clarke's column) escaped completely. The interstitial infiltration also seemed to avoid this area. However, in some sections a few of the cells of the dorsal nucleus and also some of the cells of the posterior horn showed chromatolysis and neuronophagia and were surrounded by inflammatory infiltration.

The medulla showed a patchy infiltration which, however, was largely confined to an indefinite area of gray matter on either side of the midline, spreading laterally in the dorsal third of the section. In this area many cells showed solution of granules and some degree of neuronophagia. The cells of the olivary nuclei were normal. A group of cells near the mesial plane and ventral to the central canal showed marked degeneration. These were in all probability cells of the hypoglossal nucleus.

News and Comment

INTERNATIONAL NEUROLOGICAL CONGRESS

The preliminary program of the International Neurological Congress to be held at Berne, Switzerland, from Aug. 31 to Sept. 4, 1931, is as follows:

Monday, August 31, 9: 30 a. m.

Opening Address: Prof. B. Sachs, New York.

Address of Welcome: M. Heinrich Haberlin, President of the Swiss Confederation.

SCIENTIFIC SESSION

I. Symposium: Diagnostic and Therapeutic Procedures (Surgical and Otherwise) in Brain Tumors. Chairman, Prof. Max Nonne.

Clinical Symptomatology

1. Clinical Symptomatology of Brain Tumors (20 minutes). Sir James Purves-Stewart, London.
2. Title to be submitted later (10 minutes). Clovis Vincent, Paris.
3. Title to be submitted later (10 minutes). Guiseppe Ayala, Rome.
4. Tumors of Temporo-Sphenoidal Lobes: Subfrontal Syndromes (10 minutes). Foster Kennedy, New York.

Histological Diagnosis

5. Histological Diagnosis of Tumors of the Brain (15 minutes). Percival Bailey, Chicago.
6. Tumors of the Sheaths of the Nervous System (10 minutes). Wilder Penfield, Montreal.
7. Die Bedeutung der Hirnpunktion für die Diagnose der Hirntumoren (10 minutes). Bertold Pfeifer, Nietleben.

Roentgenological Diagnosis

8. Uebersictliche Darstellung bei intrakraniellen Tumoren sich ergebenden Röntgenbefunde (10 minutes). Arthur Schüller, Vienna.
9. The Importance of Roentgenological Studies to the Neurological Surgeon (10 minutes). Ernest Sachs, St. Louis.
10. Tumoren der hinteren Schädelgrube (10 minutes). H. W. Stenvers, Utrecht.

Ventriculography and Encephalography

11. Die Ventriculographie bei den Tumoren der Grosshirnhemisphären und der Hinteren Schädelgrube (10 minutes). L. Guttman, Breslau.
12. Ventriculographie bei den Tumoren des mittelund zwischenhirns und bei Pseudotumoren (20 minutes). Otfrid Foerster, Breslau.
13. Clinical Results with Encephalography and Ventriculography (10 minutes). Francis C. Grant, Philadelphia.
14. Arterielle Jodinjektion (10 minutes). Egas Moniz, Lisbon.

Sero Diagnosis

15. Die Liquordiagnostik der Hirntumoren (15 minutes). Victor Kafka, Hamburg.
16. The Cerebrospinal Fluid in the Differential Diagnosis of Brain Tumor (10 minutes). Frank Fremont-Smith, Boston.
17. Die Erkennung von Hirntumoren durch elektrische Widerstandsbestimmung (10 minutes). H. Bohnenkamp and J. Schmän, Wurzburg.

Monday, August 31, 3: 00 p. m.

Chairman, Prof. G. Marinesco

Surgical Therapy

18. A Summary of Experiences with a Series of 2,000 Histologically Verified Intracranial Tumors (30 minutes). Harvey Cushing, Boston.
19. Title to be submitted later (15 minutes). Thierry de Martel, Paris.
20. Ueber das operative Vorgehen bei Tumoren der Vierhügel gegend (15 minutes). Otfrid Foerster, Breslau.
21. Die Gliome der Grosshirnhemisphären (10 minutes). H. Olivecrona, Stockholm.
22. The Pathology, Diagnosis and Treatment of Intrasellar Lesions (10 minutes). Charles H. Frazier, Philadelphia.
23. Traitement opératoire des gliomes du cerveau (10 minutes). Ludwig Puusepp, Tartu, Esthonia.

Radiation Treatment

24. La radiothérapie des tumeurs de l'encéphale (15 minutes). Antoine Béclère, Paris.
25. Treatment of Intracranial Tumors by Radium (10 minutes). Hugh W. Bell Cairns, London.
26. Behandlung bei Hypophysentumoren (10 minutes). O. Hirsch, Vienna.

Organotherapy

27. Organotherapy of Brain Tumors (10 minutes). Tracy J. Putnam, Boston.

Tuesday, September 1, 9: 30 a. m.

II. Symposium: Muscle Tonus, Anatomy, Physiology and Pathology. Chairman, Sir Charles Sherrington, London.

Anatomy

1. The Nuclei and Fiber Tracts Concerned in the Postural Reaction Elicited by Stimulation of the Mesencephalic Tegmentum (15 minutes). Stephen W. Ranson, Chicago.
2. On the Tonus Tracts and Their Terminal Plates in Muscle (15 minutes). Ken Kuré, Tokyo.

Experimental Physiology

3. Les facteurs régularisant le tonus musculaire (10 minutes). G. G. J. Rademaker, Leyden.
4. Tonic Responses from the Midbrain (10 minutes). T. Graham Brown, Cardiff.
5. Der Einfluss des Sympathikus auf den Muskel und eine Analyse seines Mechanismus (10 minutes). Leon Asher, Berne.
6. Sur les rélations entre l'excitabilité neuromusculaire et le tonus (10 minutes). G. Marinesco, Bucarest.
7. The Part Played by Afferent Muscular Nerve Endings in Postural (Tonic) Reflexes (10 minutes). D. Denny-Brown, London.
8. Elektrische Analyse des Tonus (10 minutes). V. von Weizsacker, Heidelberg.
9. Muscle Tonus and Chronaximetry (15 minutes). M. Kroll and D. Markow, Minsk, Russia.

Pharmacology

10. Pharmacologie du tonus musculaire (10 minutes). F. Bremer, Brussels.
11. On the Pharmacology of the Tonus Centers (10 minutes). E. A. Spiegel, Vienna.

Pathology

12. On the Relation of Modifications of Muscle Tonus to Interruption of Certain Anatomical Pathways (15 minutes). Lewis J. Pollock and Loyal Davis, Chicago.

Clinical

13. Disorders of Tone at Different Physiological Levels (15 minutes). S. A. K. Wilson, London.
14. Ipertonie precoci e sistema extrapyramidale (10 minutes). V. M. Buscaino, Catania.
15. The Static and Kinetic Systems and Their Relation to Muscle Tone (10 minutes). Ramsay Hunt, New York.
16. Rélations du tonus musculaire avec le syndrome parkinsonien (10 minutes). R. Cruchet, Bordeaux.
17. Altérations du tonus musculaire dans les syndromes extrapyramidaux (10 minutes). F. Negro, Turin.
18. Le phenomène de la poussée (10 minutes). A. Thévenard, Paris.
19. Concluding Remarks. Sir Charles Sherrington, Oxford.

Tuesday, September 1, 3:00 p. m.

SECTION A. NEUROLOGICAL SURGERY. Chairman, PROF. MONRAD-KROHN.

1. Die Operabilität der intramedullären Rückenmarkstumoren (20 minutes). Prof. A. C. Eiselsberg, Austria.
2. Some Phases of the Surgical Indications for Sympathetic Ganglionectomy and Ramisectomy in the Treatment of the Various Vascular Diseases, as Raynaud's Disease, Selected Cases of Thrombo-Angiitis Obliterans, and Scleroderma and Arthritis (15 minutes). Alfred W. Adson, United States.
3. Die Bedeutung der bioptischen Methoden für die Diagnose der Tumoren des Centralnervensystems (15 minutes). E. Forster, Germany.
4. Eine Studie über respiratorische und pulsatorische Schwankungen des Liquordruckes und ihr Verhalten bei spinalen Block. N. Antoni, Sweden.

Therapy

5. Weitere Erfahrungen mit der Malaria-Therapie bei metaluetischen Erkrankungen (20 minutes). J. Wagner von Jauregg, Austria.
6. Tryparsamide and Neurosyphilis (15 minutes). Hans M. Reese, United States.
7. The Treatment of Syringomyelia (15 minutes). Henry Cohen, England.
8. Les résultats du traitement de la sclérose en plaques par la radiothérapie (15 minutes). Herman Eufemjusz, Poland.

SECTION B. CLINICAL NEUROLOGY. Chairman, PROF. ROBERT BING, Basel.

1. A Study of Aphasia with an Attempt to Formulate New Tests. Theodore H. Weisenburg, United States.
2. Speech in Animals and Children and Its Integration with Intelligence. Michael Osnato, United States.
3. Sull'aprassia di Liepmann. Fragnito, Italy.
4. A Contribution to the Differential Diagnosis of Chiasmal Lesions. Norman M. Dott, England.
5. Das Symptom der Seelenblindheit und seine cerebrale Mechanik. Niessl von Mayendorf, Germany.
6. Color Vision, Color Agnosia and Their Localization. I. S. Wechsler, United States.

7. An Experimental Investigation on the Effect of Alcohol and Other Agents upon the Perception of Color. K. Zeiner-Henrikson, Norway.
8. Le syndrome migraino-tétanique. Wladyslaw Sterling, Poland.
9. L'accroisement progressif des affections nerveuses et psychiques en Grèce et le polymorphisme de l'alcoolisme médullaire. M. Catsaras, Greece.
10. Sur la diagnostic précoce de la sclérose en plaques. Rodriguez-Arias, Spain.

SECTION C. CLINICO-PATHOLOGY. Chairman, PROF. AUGUSTE WIMMER.

1. Rôle des compressions osseuses dans les paraplégies pottiques. Étude anatomo-pathologique et clinique. Mme. Sorrel-Dejerine and E. Sorrel, France.
2. La maladie de Korsakow (étude étiologique et anatomo-pathologique). H. Marcus, Sweden.
3. Pathological-Anatomical Investigations of Cases of Encephalo-Myelitis Disseminata Acuta (Neuraxitis focalis acuta). K. Kahlmeter, Sweden.
4. Zur Klinik und Histopathologie der diffüsen Tumorbildung des Centralnervensystems. F. Schob, Germany.
5. Ein Dystoniefall mit anatomischen Befund. H. von Halban, Poland, and E. Pollak, Austria.
6. Kann man alte Rindendefekte traumatischer und arteriosklerotischer Genese von einander unterscheiden? Die Bedeutung des "état vermoulo." H. Spatz, Germany.
7. Parkinsonismo encefalitico e lesioni cortico-nigriche. Prof. A. Donaggio, Italy.

Tonus

8. Tonus musculaire psycho-moteur. H. Claude and H. Baruk, France.
9. Sul tono dei muscoli mimici in alcune condizioni morbose. Prof. T. Senise, Italy.
10. Sur la participation du système sympathique dans le mécanisme du tonus musculaire. J. Sebec, Czechoslovakia.
11. L'appareil vestibulaire et le tonus musculaire. T. Dosuzkov, Czechoslovakia.
12. Contributo alla patologia del tono muscolare. Pfanner, Italy.

Wednesday, September 2

Excursion to Interlaken and the vicinity.

Thursday, September 3, 9: 30 a. m.

III. SYMPOSIUM: LES INFECTIONS AIGUËS NON-SUPPURATIVES DU SYSTÈME NERVEUX. Chairman, PROF. GEORGES GUILLAIN.

Pathologie Générale

1. Introduction à la pathologie générale des infections aiguës du système nerveux (20 minutes). Otto Marburg, Vienna.
2. Pathogénie de certaines encéphalo-myélites à ultra-virus (20 minutes). Georges Marinesco and St. Draganesco, Bucarest.

Anatomie Pathologique

3. Anatomie pathologique générale des infections aiguës du système nerveux (20 minutes). J. Godwin Greenfield, London.
4. Die Bedeutung der Einschlusskörperchen bei den sogenannten Viruskrankheiten (10 minutes). F. H. Lewy, Berlin.
5. Sur le mécanisme et les conséquences de la lyse myélinique dans certaines infections à virus neurotrope (10 minutes). L. Cornil, Marseilles.
6. Contribution histopathologique à l'étude de la sclérose en plaques aiguë (avec projections) (15 minutes). R. A. Ley, Bruxelles, and Ludo van Bogaert, Anvers.
7. Strukturelle Veränderungen der Nieren bei Allgemein-Infektionen, die sich nach Durchschneidung der entsprechtenden vegetativen Nerven verhindern lassen (10 minutes). E. F. Müller, Hamburg.

Études Cliniques

8. Études cliniques générales dans les infections du système nerveux céntral (10 minutes). Auguste Wimmer, Copenhagen.
9. Rage, Maladie de Borna; Paralysie de Landry (10 minutes). H. Pette, Hamburg.
10. Zona: Les infections herpétiques (15 minutes). André-Thomas, Paris.
11. Encéphalite vaccinale, encéphalite varicelleuse. Cas non-classifiés (10 minutes). L. van Bogaert, Anvers.
12. Questions psychiatriques et biologiques en connexion avec les infections du système nerveux (20 minutes). V. M. Buscaino, Catane.
13. Bemerkungen zur Frage der epidemischen Encephalitiden (10 minutes). C. von Economo, Vienna.
14. L'épidémiologie de l'encéphalite épidémique (10 minutes). M. Chassanno, Minsk.
15. Ueber die infektios-toxische Genese pseudo-neurasthenischer Krankheitsbilder aus dem Formenkreis der Encephalitis lethargica (Economo) (10 minutes). M. G. Reid, Schwerin, I. M.
16. Forschungsvergebnisse bei multipler Sklerose (10 minutes). M. Steiner, Heidelberg.
17. La sclérose en plaques aiguë (10 minutes). T. Alajouanine, Paris.
18. Évolution clinique atypique de l'encéphalo-myélite, de la sclérose en plaques et de la sclérose latérale amyotrophique (10 minutes). M. Paulian, Bucarest.
19. Toxic Encephalopathy in Measles (10 minutes). A. Ferraro and I. H. Scheffer, New York.
20. Formes cliniques de la maladies de Heine-Medin chez l'adulte (10 minutes). M. Étienne, Nancy.
21. Discussion clinique de differentes symptomes de la paralysie infantile (10 minutes). J. A. Barré, Strasbourg.
22. Cas de myélite subaiguëe d'origine infectieuse cryptogénétique 10 minutes). I. Minea, Cluj.
23. La disposition et la constellation dans l'origine des maladies infectieuses du système nerveux (10 minutes). N. Gourevitsch and D. Rosenstein, Moscow.
24. Maladies infectieuses du système nerveux (10 minutes). Dr. Beletzki, Moscow.
25. Conclusions. Georges Guillain, Paris.

Thursday, September 3, 3 p. m.

SECTION D. BRAIN TUMOR AND ALLIED SUBJECTS. Chairman, PROF. KARL SCHAFFER.

1. Hallucinations visuelles au cours des tumeurs cérébrales. J. Christophe and P. Schmite, France.
2. Zur Frage der Stirnhirnataxie, insbesondere bei Hirntumoren. R. Brun, Switzerland.
3. Ueber das Stirnhirn Syndrom. Josepf Gerstmann, Austria.
4. Tumors of the Cerebellum. Debrochotow, Russia.
5. Disorders of Optic Nystagmus Due to Cerebral Tumors. James C. Fox, Jr., United States.
6. Sur quatre cas d'épilépsie avec tumeur de Lindau. C. I. Urechia, Roumania.
7. Contributo alla diagnosi differenziale tra tumor cerebri e meningite sierosa. E. Medea, Italy.
8. Eine neue Methode zur Lokalisation von Gehirntumoren mittels perkutorischer Transsonanz (Tonfilm-Vorführung). Ladislaus Benedek, Hungary.
9. Sui meccanismi dei disturbi postpuntori e sulla pericolosità della puntura lombare nei casi di tumore endocranice. W. G. Boschi, Italy.

SECTION E. NEURO-PATHOLOGY. Chairman, PROF. OTTO MARBURG, Vienna.

1. Die pathologische Anatomie und die Pathogenese der Rückenmarkstumoren. Gustave Wangel, Finland.
2. Les principales variétés des tumeurs gliomateuses, leur fréquence relative, leur siège et leur répartition suivant l'age des malades. Quelques types de tumeurs non-indentifiables (10 minutes). Gustave Roussy and C. Oberling, Paris.
3. Spongioblastoma Multiforme: Further Observations on Some of Its Distinctive-Structural Features and on the Position It Holds Among Other Gliogenous Tumors of the Nervous System. Joseph H. Globus and Israel Strauss, United States.
4. Peculiar Gliomas of the Brain. I. Oljenick, Holland.
5. Histologische Forschungen über den Einfluss der Roentgenbehandlung bei Gehirngliomen. J. Mackiewicz, Poland.
6. Fungus Infections of the Central Nervous System. Walter Freeman, United States.
7. Au sujet d'une maladie du cerveau humain non observée jusqu'à ce jour et produit par la coccydié (?). Lopez-Albo, Spain.

Infection

8. Entzuendung im Centralnervensystem. L. Bouman, Holland.
9. Epidémiologie de la poliomyélite aiguë. C. Kling, Sweden.
10. Ueber Myelitis bei Pocken. B. Brouwer, Holland.
11. Zur Morphologie des Zosters. S. Ingvar, Sweden.
12. The Brain in Acute Rheumatic Fever. N. W. Winkelman and John L. Eckel, United States.

SECTION F. INVESTIGATIVE NEUROLOGY. Chairman, DR. EDWARD FLATAU.

1. Les névroses expérimentalement réproductibles chez les animaux. I. P. Pavlov, Russia.
2. Demonstration Concerning the Morphology of the Central Nervous System in Prehistoric Races. C. U. Ariëns Kappers, Holland.

3. À propos de la localisation de la conscience centrale. L. Häskovec, Czechoslovakia.
4. Zur Frage der zentralen Repräsentation von gekreutzen und ungekreutzen Sehnervenfasern in den zentralen optischen Bahnen besonders im Corpus geniculatum externum. M. Minkowski, Switzerland.
5. Ueber die Entwicklung der zentralen optischen Bahnen. E. Frey, Switzerland.
6. Muskelatrophie nach der Exstirpation des Halssympathicus. Morisama Tsuji, Japan.
7. On the Influence of the Sympathetic Nerve on the Striped Muscles of the Frog. J. W. Langelaan, Holland.
8. Influenza della bulbocapnina sul tono muscolare. de Giacomo, Italy.
9. The Cerebellum: The Effect of Focal Lesions on Muscle Tone. Aubrey T. Mussen, United States.
10. Experimental Convulsions Following Head Injuries. S. Bernard Wortis, United States.
11. Lehrfilm über die Bewegungsstörungen der unteren Extremitäten. de Quervain, Switzerland.
12. Ein Phänomen bei dem ein rhythmisches Spiel von antagonistischen zentralen Nervenimpulsen entoptisch wahrnehmbar ist. G. Goethlin, Sweden.

SECTION G. CLINICAL NEUROLOGY. Chairman, DR. F. SANO.

1. Ensemble de remarques sur le signe de Babinski. A. Tournay, France.
2. Le syndrome neurologique des états de stupeur. G. Bychowski, Poland.
3. Beobachtungen über gegenseitige Beziehungen des Lachens, Orgasmus, Tonusverlust und Schlafsucht. J. Rothfeld, Poland.
4. Das Verhältniss der Splenohepatomegalie zur amaurotischen Idiotie. Karl Schaffer, Hungary.
5. Picksche Krankheit. K. H. Bouman, Holland.
6. Die Tay-Sachs'sche Form der amaurotischen Idiotie in ihrer Beziehung zur phosphatidzelligen Lipoidose im Gehirne bei Niemann-Pickscher Krankheit. Emil Epstein, Austria.
7. Zur Frage der nosologischen und lokalisatorischen Auffassung der Torsionsdystonischen Krankheitserscheinungen. A. Jakob, Germany.
8. Ueber den Hemiballismus. Michael Nikitin and A. L. Polenoff, Russia.
9. Ueber die Wernicke'sche Krampusneurose. Josef Wilder, Austria.
10. Syndrome of Rising Intracranial Pressure of Functional Origin. Monachow, Russia.
11. Das traumatische Oedem. Brauecker, Germany.

Friday, September 4, 9: 30 a. m.

IV. SYMPOSIUM: THE RÔLE OF TRAUMA IN THE PRODUCTION OF NERVOUS SYMPTOMS. Chairman, PROF. OTTORINO ROSSI, Pavia.

1. Linee fondamentali di traumatologia del systema nervoso centrale impostazione delle principali questioni riguardanti i meccanismi di azione del trauma sul sistema nervoso (20 minutes). Ottorino Rossi, Pavia.
2. Commotio cerebri: Diagnosis and Treatment of the Cerebral States Following Head Injuries (Exclusive of Ordinary Brain Injuries) (15 minutes). C. P. Symonds, London.
3. Grundlinien des Referates über der Einfluss des Traumas bei der Genese einiger Nervenkrankheiten. O. Veraguth, Zurich.

4. Altérations de la neuroglie consécutives aux traumatismes (15 minutes). P. del Rio Hortega, Madrid.
5. Rapport sur les syndromes neurologiques consécutifs aux électrocutions industrielles (15 minutes). F. Naville, Geneva.
6. Commotion de la moelle épinière (15 minutes). Jean Lhermitte, Paris.
7. Mikrostructurelle traumatische Veränderungen des Nervensystems im Lichte der Kriegserfahrungen (15 minutes). Arthur von Sarbo, Budapest.
8. The Traumatic Neuroses Considered at the Psycho-Sociological Level (15 minutes). Smith Ely Jelliffe, New York.
9. Conclusions. Ottorino Rossi, Pavia.

Friday, September 4, 3 p. m.

SECTION H. INVESTIGATIVE NEUROLOGY. Chairman, PROF. C. U. ARIËNS KAPPERS.

1. Sur le sommeil expérimental produit par une action sur la région du diencéphale et du troisième ventricule (avec projections). G. R. Lafora and J. Sanz, Spain.
2. Centrale und periphere Innervation der innersekretorischen Druesen. L. Pines, Russia.
3. The Effect of Myelolytic Toxins on Nervous Tissue. Arthur Weil, United States.
4. Pathogenic Factors in Some Diseases of Myelin. Richard M. Brickner, United States.
5. Ueber die Beziehungen zwischen Hirn- und Schaedelentwicklung. Weygandt, Germany.
6. The Termination of the Pyramidal Tract in Man. J. P. Martin, England.
7. Chronaximetrie im vegetativen Organgebiet. Stein, Germany.
8. La barrière protectrice meningée et le système reticulo-endothélial. Mme. Nathalie Zand, Germany.
9. Alcuni dati clinici e sperimentali deponenti per l'ammissione di un centro vegetativo epilettogeno nella regione diencefalica. Alberto Salmon, Italy.
10. Physiologische Versuche über Katalepsie. H. de Jong, Holland.
11. Die neueren Methoden zur Messung des Dehnungswiederstandes und der Reibung im menschlichen Muskel. G. Schaltenbrand, Germany.
12. Ueber die Rolle des Cortex bei der Bulbokapninkatalepsie (10 minutes). F. Krause, Germany.

SECTION K. CLINICAL NEUROLOGY. Chairman, PROF. L. MINOR.

1. Syndromes of the Superior Cerebellar Artery. Macdonald Critchley, England.
2. On the Cerebellar Function. F. Leiri, Finland.
3. The Influence of Calcium Deprivation on the Autonomic Nervous System. Walter Timme, United States.
4. Intracranial Venous Thrombosis. F. R. Ferguson, England.
5. Premonitory Headaches in Leaking Aneurysm. W. J. Adie, England.
6. Essai de synthèse de toutes les affections myopathiques à l'aide de la chronaxie. G. Bourguignon, France.
7. Distonia da torsione. Poppi, Italy.
8. Demonstration of Typical and Atypical Extrapyramidal Arm Reflexes Produced by Faradic Irritation of the Hands (Film Illustration). T. Wernoe, Denmark.

9. Ueber Stoerungen innerer Organe bei Syringomelie. Leo Hess and Josef Faltitschek, Austria.
10. Ueber humorale Herznervenwikung. K. Hausen, Germany.

SECTION L. TRAUMA. Chairman, PROF. HENRY MARCUS.

1. Trauma. G. H. Monrad-Krohn, Norway.
2. Sur les séquelles nerveuses dans les traumatismes. O. Crouzon, France.
3. Decerebrate Rigidity in Head Injury. Geoffrey Jefferson, England.
4. L'influence du traumatisme dans les infections du névraxe. M. Laignel-Lavastine, France.
5. Epilessia Jacksoniana post-traumatica; criteri di cura chirurgica razionale. R. Alessandri, Italy.
6. Du rôle du traumatisme dans la production des différentes affections. J. A. Barre, France.
7. Zur Differentialdiagnose organisch-psychischer und psychogen bedingter Störungen nach Schaedel- und Hirntraumen vermittels des Rorsch'scher Formdeutversuche. E. Oberholzer, Switzerland.
8. Persistierende Liquorveränderungen nach früheren Traumata Capitis. R. Eeg-Olofsson, Sweden.
9. The Pathogenetic Rôle of Trauma in Neuropsychic Disturbances. Futer and Taranow, Russia.
10. Sui rapporti patogenetici fra i traumatismi e alcune affezioni del sistema nervosa. G. Catola, Italy.
11. Die Objektivierung post-commotioneller Beschwerden durch das Encephalogramm. Hauptmann, Germany.

SECTION M. LES INFECTIONS AIGUËS NON-SUPPURATIVES DU SYSTÈME NERVEUX (Concluded). Chairman, PROF. A. AUSTREGESILO, Paris.

Friday, September 4, 9 p. m.

A conference (smoker), open to all, will be held with Prof. B. Sachs as presiding officer. The subject will be "The Relation of Neurology to General Medicine and Psychiatry in Universities and Hospitals," and the speakers: Professor Minkowski, Switzerland; Prof. T. H. Weisenburg, United States; Prof. S. A. K. Wilson, Great Britain; Prof. Dr. L. Häskovec ("La réforme de l'étude médicale et le besoin des cliniques neurologiques spéciales"), Czechoslovakia; Prof. G. Guillain, France, and Prof. C. von Economo, Austria.

SCHWEIZER ARCHIV FÜR NEUROLOGIE UND PSYCHIATRIE

The publication of this journal, momentarily stopped by the death of Prof. C. von Monakow in October, 1930, has now been resumed under the direction of four associate editors, Prof. R. Bing of Basle and Prof. M. Minkowski of Zürich representing neurology, and Prof. Hans W. Maier of Zürich and Dr. H. Steck of Cery-Lausanne representing psychiatry. Art. Institut Orell Füssli, Zürich, will continue the publishing. Because of the delay caused by this reorganization the first issue for the year 1931 (vol. 27, part 1) will not appear until May or June.

Obituary

FRANCIS X. DERCUM, M.D.
1856-1931

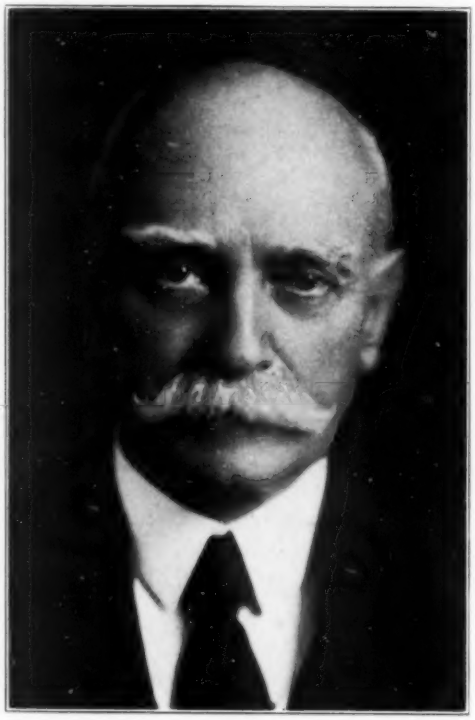
The sudden death of Dr. Francis X. Dercum on April 23, 1931, occurred as he was presiding at the annual meeting of the American Philosophical Society. It was understood that his health had been somewhat impaired, but he had gone to the meeting without a sign of suffering, and with anticipation of a program of unusual interest. His death came as a shock to his many friends.

Dr. Dercum was born in Philadelphia on Aug. 10, 1856, of German parentage, and after graduating at high school in 1873, he entered the University of Pennsylvania and took his degree in medicine in 1877. He early began to show an interest in diseases of the nervous system and in problems of physiology and evolution; he was inspired especially by the teachings of Chapman, Wood and Leidy. His range of scientific interests was shown by his membership in the Academy of Natural Sciences. He was appointed instructor in neurology and chief of the nervous disease clinic in the University Hospital, where his work first brought him into notice as a specialist in clinical neurology. In 1884, he joined Dr. Charles K. Mills, Dr. Wharton Sinkler, Dr. J. T. Eskridge and others in founding the Philadelphia Neurological Society. The idea of such a society had first occurred to Dr. Mills, and its foundation may be said to mark the beginning of a distinct era in neurology in Philadelphia. The society had for its first president Dr. S. Weir Mitchell, and from its organization it has had a record of continued activity and usefulness. Dr. Dercum was always one of its most active supporters, a frequent contributor to its proceedings, and twice served as its president. The members of the society will all feel that in his death they have lost one of their most distinguished colleagues.

Especially noteworthy in Dr. Dercum's career was his service on the staff of the nervous disease wards of the Philadelphia General Hospital. This department of the hospital became one of the largest neurologic clinics in the country, and it was there that Dr. Dercum made some of the original observations with which his name is associated. In those early days, as ever since, the Blockley service was the training field of many Philadelphia neurologists. It offered by reason of its many beds and large variety of cases a quite unequaled opportunity, and those who served there will always remember it as the scene of enthusiastic work and profitable association. Dr. Dercum was appointed to the staff a

few years after the service was organized. The case in which the condition occurred that he called "adiposis dolorosa," and that has since borne his name, was seen in his wards.

In 1892, Dr. Dercum was appointed clinical professor of mental and nervous diseases in Jefferson Medical College, a post which he held with marked ability until 1925, when he resigned. As a clinical teacher he had a clear and concise method, an abundant experience and a forceful personality. During his occupancy of this chair his practice



FRANCIS X. DERCUM, M.D.
1856-1931

extended as a specialist and consultant. As is well known, he was called in consultation in the case of President Woodrow Wilson. He was also frequently engaged as an expert in medicolegal and civil suits in the courts.

Dr. Dercum received a distinguished honor in being elected president of the American Philosophical Society, a society which dates its origin far back in colonial times and devotes its activities to the advancement of science. It has numbered on its list many eminent names. At one time he had started a plan to build a new hall on the Parkway, but

among his last acts he is said to have advised that the society should not move from its old historic hall on Independence Square.

Dr. Dercum was always active in literary work in his specialty, and he contributed many valuable papers to various journals. In 1895, he edited a "Text Book on Nervous Diseases" by American authors, a representative book of neurology in this country at that time. He wrote a "Clinical Manual of Mental Diseases" in 1913, and a work on "Rest and Suggestion" in 1917, and later the "Biology of the Internal Secretions." His most philosophic work was the "Essay on the Physiology of Mind," in which the aim was to correlate the mental functions with the morphology and physiology of the brain. As an author, Dr. Dercum had a good style and a comprehensive grasp of his subject, based on a wide study both in the clinic and laboratory as well as in the literature of his specialty.

Dr. Dercum received many honors. He was a corresponding member of the Neurological Society of Paris, honorary member of the Psychiatrical and Neurological Society of Vienna, corresponding member of the Neurological Section of the Royal Society of Medicine of London, and Chevalier de la Legion d'Honneur.

He was a Fellow of the College of Physicians of Philadelphia, and member of the American Neurological Association, of which he had been president; he was also a member of numerous local societies and clubs, among which was the Wistar Association, a social club of long standing. His varied interests were shown by his membership in the Franklin Institute, the Academy of Natural Sciences and the Historical Society of Pennsylvania.

The death of Dr. Dercum removes from our midst a distinguished scientist, a beloved physician and a valued friend. To his old associates especially, his loss adds to the sad changes of the passing years.

JAMES HENDRIE LLOYD, M.D.

Abstracts from Current Literature

THE COCHLEAR REFLEXES AND THEIR SEMEIOLOGIC VALUE. J. HELSMOORTEL, JR., and RENÉ NYSSEN, J. de neurol. et de psychiat. **30**:681 (Nov.) 1930.

For years, efforts have been made to devise a method of obtaining cochlear reflexes to auditory stimulation without the voluntary participation of the subject examined. These efforts were stimulated by the harvest of cases of organic, psychic, simulated and exaggerated deafness resulting from the World War. All reactions of the cochlea to stimulation are not fitted for practical clinical use, e. g., the tensor tympanic and the auricular reflex.

General muscular reaction to loud sounds was studied by Cemach, and Sommer devised a method of graphically registering these movements.

The cochleopalpebral reflex is much more constant than the general muscular response to cochlear stimulation and has had a wide clinical use. Hogyes, basing his statements on experiments on rabbits, in which he found that the cerebral cortex does not participate in the cochleo-auricular reflex and that the latter fails only after the destruction of the middle cerebellar peduncles, believed that, in man, the reflex cochlear excitability does not necessarily disappear with the loss of acoustic sensibility.

Among others, Bechterew, Gault, Falta, Belinoff, Wodak and Cemach made systematic and exhaustive studies of the cochleopalpebral reflex, employing various methods of production of sound, and arrived at varying conclusions as to its value. The authors accept the dictum of Cemach that, to avoid error, the source of the sound must be at a distance from the ear. Otherwise, a reaction is possible even in completely deafened persons, owing to extracochlear excitation. They have found also that intense, though not painful, sounds produced in contact with the ear cause an increase of arterial tension in cases of absolute labyrinthine deafness equal to that found in subjects with normal hearing. Certain noncochlear excitations (tactile, caloric) applied in the external auditory canal or in the concha, are capable of causing a palpebral reaction; and in persons with normal hearing and in those completely deafened, a slight displacement of air in the concha almost constantly causes a palpebral reflex. The vocal cord reflex (Muck) is less reliable than the cochleopalpebral or the cochleopupillary reflex. In the psychogalvanic reflex, an electric current passing through the subject is augmented temporarily by psychic excitations, and such changes are detected by the oscillations of a galvanometric mirror. These excitations produce in the organism certain physical changes which are due to nervous, secretory, muscular, sanguine and lymphatic modifications and, probably especially, to secretory modifications of the cutaneous glands and to vasomotor phenomena. All the sense organs may constitute the receptive surface for the psychogalvanic reflex, but only the auditory sense is considered here. From a study of this reflex, Albrecht concludes that it permits a differentiation between organic and functional deafness, but it does not enable one to distinguish psychic from simulated deafness. Van Iterson continued Albrecht's experiments and has photographed the curves of the psychogalvanic reflex. He used as auditory stimuli, speech, tuning forks, the Galton whistle and explosions. He expressed the belief that the intensity of the reaction depends, not on the degree of cochlear excitability, but on the psychic modifications produced in the subject.

Several investigators have tried to find in the circulatory modifications produced by auditory excitations, objective criteria for cochlear excitability. Wiersma registered simultaneously respiratory, psychogalvanic and plethysmographic changes under the influence of the sound of an electric bell. During the mobilization in Holland, he was able to detect a simulated, or to confirm a real, deafness.

The authors used the plethysmographic technic of Wiersma. Most investigators agree that peripheral vasoconstriction is by far the most frequent vasomotor reaction, independent of the psychic quality of the stimulus that inaugurates it. The reaction consists of a slight rise of short duration in the curve immediately after the stimulus, followed by a more or less prolonged volumetric diminution. In subjects who react by a general muscular contraction, there is a sharp rise in the curve immediately following the excitation. Great care was used to avoid extracochlear excitations. Normal subjects, patients with complete labyrinthine deafness and those with residual hearing were tested. Of thirty-three normal persons, twenty-three reacted to different kinds of auditory stimuli; ten who showed no reaction had a small pulse amplitude, and it was assumed that their vessels were in a state of spastic contraction and hence were incapable of an increase of spasm. The stimulus used was the noise apparatus of Zund-Burguet, placed 4 cm. from the ear. It was discovered that at this distance tactile impressions were transmitted. Among six subjects, four gave positive reactions when the same stimulus was removed to 1 m., the fifth reacted at a distance of 50 cm. and the sixth at 16 cm. The fact that the subjects were warned beforehand of the impending sound and the fact that, in some cases, the sound was produced at regular intervals had no influence on the intensity of the reactions.

Of eight persons with complete bilateral deafness, only one reacted positively, and it is supposed that this reaction was due to a tactile stimulus. Three persons with residual hearing were examined. When there was good hearing in one ear, the test was not conclusive, owing to the impossibility of shutting out sounds from this ear. No patients with bilateral psychic or simulated deafness were examined.

The authors conclude that, in cases with positive reactions, the plethysmographic method allows one to determine approximately the degree of cochlear excitability and to establish whether the subject is capable of hearing the spoken voice. Even an insignificant residue of hearing can suffice to inaugurate the vasomotor reflex. Absence of reaction does not mean absence of cochlear excitability, since psychic or vascular conditions may prevent vasoconstriction. The will of the patient is without effect on the reaction. If the cochlear reflexes are present, they constitute incontestable evidence of auditory excitability. Intense stimuli easily pass the threshold of residual cochlear excitability, but the intensity of the reaction is not proportional to the intensity of the auditory impression. The intensity of the reaction depends on numerous factors: the general reflectivity of the patient, his attention, the degree of his emotional upset, and the state of the muscles, iris, skin or the vessels that are the seat of the reaction. The general muscular reflex, the cochleopalpebral reflex, Muck's reflex, the cochleopupillary reflex and even the psychogalvanic and plethysmographic reflexes to noises and sounds can only inform one that the hearing is not completely lost; they cannot evalute the degree of auditory acuity. If the subject pretends to hear nothing, the determination of cochlear excitability does not exclude a possible organic cause for the pretended deafness. The researches of Hogyes and others point to the conclusion that certain cochlear reflexes are not necessarily allied to the function of the auditory centers. If a central lesion can be excluded, auditory excitability, established by the existence of the cochlear reflexes when the subject pretends to hear nothing, does not allow one to determine whether one is dealing with hysteria or with simulation or conscious exaggeration. In certain cases the differential diagnosis will be difficult, and it must be kept in mind that a conscious and intentional simulation is not incompatible with a demonstrated hysteria.

It is otherwise in the psychogalvanic reactions to speech. Since speech acts through the intermediary of a psychic process, these reactions furnish a means of testing the subject's capacity for hearing and understanding the voice at different distances.

Acoustic reflexes can fail to occur in spite of a normal auditory acuity. The deduction from this fact is that only positive cochlear reactions warrant definite conclusions as to the presence of auditory excitability. If one of the described

reflexes is absent, Corti's organ must be interrogated through other reflexes. It has been ascertained for example that certain persons react by a pupillary but not by a palpebral reflex. In certain cases of hysteria, Wiersma obtained a psychogalvanic reaction while the plethysmogram remained unchanged. But, taking into account all the reservations, the reflex method will be useful in all cases in which it is impossible to agree with the statements of the subject.

DENNIS, Colorado Springs, Colo.

DIFFUSE HAMARTOMA (GANGLIONEUROMA) OF THE CEREBELLLUM AND ITS GENESIS. MAX BIELSCHOWSKY and ARTHUR SIMONS, J. f. Psychol. u. Neurol. **41**:50, 1930.

Ganglioneuromas are rare blastomas most commonly found in the sympathetic nervous system. No more than a dozen verified cases are reported in the literature. Of these, five are cases of solitary, one of multiple and three of diffuse tumors, and the other three comprise the subject of this communication. These tumors belong to the mature forms of neuroma. The fact that, in addition to the coarse network of myelinated and nonmyelinated nerve fibers, they also contain polynuclear ganglion cells cannot be regarded as evidence that in these tumors one is dealing with a neoplastic proliferation of the ganglion cells; the latter may be residua of an incomplete cellular division during fetal life.

The ganglioneuromas of the cerebellum described in this paper differ markedly in structure from those hitherto reported. Macroscopically, they can be recognized by the enormous, uniform increase in volume of extensive portions of the cerebellar hemispheres and vermis. Clinically, the cases ran the course of tumor of the brain with general signs of increased intracranial pressure.

Histologically, even under a low power lens, the enormous width of the molecular zone with the complete absence of the granular zone and the unusually scanty medullary layer was striking. The medullary lamellae showed in some areas stripes of delicate glial structure traversed to a great extent by axis-cylinders and partly also by a small number of medullated nerve fibers. In some areas these "empty" lamellae contained a loose gutter-like arrangement of connective(?) tissue consisting of many thin-walled vessels; frequently, however, these areas were replaced by slitlike cavities that had apparently been filled with fluid. The molecular zone contained accumulations of concretions and pseudocalcified scales; delicate and coarse granular concrements were also observed in the blood vessels of this zone.

The margin of the thin medullary lamellae contained a wide cellular layer consisting of neuroblasts of various sizes and in various stages of maturity. In the different silver impregnations these immature cells showed an absence of dendrites as well as of axis-cylinders. There was no indication of any of the typical granular cells ordinarily found in this layer, nor were there present any typical Purkinje cells; instead of the latter, however, there were isolated large ganglion cells, the size of which greatly exceeded that of the usual Purkinje cells.

Myelin sheath preparations showed only a few nerve fibers in the "germinal layer" in contrast to the large number of fibers in the protoplasmic tissue between this layer and the pial surface of the broad molecular zone proper. Normally, the latter shows merely a few myelinated fibers which are chiefly seen only near the Purkinje cells. Most of these fibers ran in a horizontal direction, crossing rectangularly those going in the vertical direction toward the pia. This was universal in all the sections examined. It differed from the normal not only by the density of structure but also by the unusual richness of the myelin content. This, the authors believe, is a pathologic production of fibers, the origin of which must be sought in the neuroblasts of the "germinal zone." It was likewise noteworthy that the axons of the immature neuroblasts were also found on the myelin sheaths. Immediately under the pia there were isolated small islets of ganglion and glia cells as well as typical granular cells of the type observed only in the granular zone in the normal adult cerebellum. In some areas these accumula-

tions of neuroblasts in the vicinity of the smaller blood vessels extended deeply into the molecular zone. In other areas with the use of silver preparations many of these neuroblasts were seen to be devoid of typical axons but to contain a coil-like formation of prolongations which were attached to the adjacent cells, reminding one of the glomerular formations observed in the sympathetic ganglia. It is probable that these coil-like prolongations are derived from the principal dendrites, and that one is dealing here with a cellular function which, developmentally, is probably closely related to that of the Purkinje cells. The occasional basket-like appearance of these "coils" and of the cells is further evidence of the likelihood of this type of genesis. The neuroblasts and their dendrites showed inclusions that were typical of the so-called Lafora's amyloid bodies.

Striking changes were also observed in the glia of all layers of the diseased cerebellar hemisphere. Here were seen giant nuclei with a delicate nuclear membrane and a marked resemblance to Alzheimer's glia nuclei of Wilson's disease and pseudosclerosis. Such cells were found not only in the cerebellum but also in the fifth cervical segment of the spinal cord. Similar histologic conditions are recorded in the vermis.

There was a corresponding diminution in the size of the noninvolved cerebellar hemisphere and of the cerebellar connections leading from it to the affected hemisphere. The nucleus dentatus could not be found on the healthy side but was well developed on the diseased side.

The cerebrum showed only preagonal edema. The cervical portion of the spinal cord, however, showed definite signs of maldevelopment—a hydromyelia, which is now generally regarded as a defective closure of the original neural tube. This is emphasized as indicating maldevelopment not only of the cerebellum but also of the spinal cord. In this connection the authors review Wilhelm E. Schmidt's case in which there was congenital hemihypertrophy of most of the bones on the left side of the head and face. This patient also had a carcinoma in the region of the left parotid with metastases at the base of the skull, spine and liver, as well as a large, centrally softened perithelioma of the left frontal lobe with considerable deformity of this portion of the brain; the left cerebellar hemisphere was unusually hypertrophied, its lobules being wider and much more prominent than normal—a true pachygyria with many heterotopies. The histologic picture of the granular and molecular zones, as well as that of the Purkinje cells, was similar to that of the cases described in this communication. The authors have no doubt that Schmidt's case was also one of hamartoma.

Bielschowsky and Simons next review the case reported by Lhermitte and Duclos and regarded by them as a neoplastic process but which was actually a case of diffuse ganglioneuroma myelinicum of the cerebellar cortex.

It is noteworthy that in the cases of ganglioneuroma thus far reported the pathologic process was an accidental discovery at necropsy. In some of the cases it was found in persons suffering from epilepsy who had died suddenly; in others it was found in cases in which the epilepsy was associated with symptoms of localizable tumor of the brain; in still others the disease was manifested by the presence of focal symptoms from the very beginning of the disease.

Clinically, the cases present no peculiarities as far as age, development, symptomatology and course of the disease are concerned. It is conceivable, however, that should puncture of the brain be indicated in any given case, a diagnosis could be established in vivo. In the nine cases reported by other observers there were two with polydactylism; in one of the cases reported in this paper there was polydactylism of the fingers, and in another polydactylism of the fingers and toes. Bearing in mind the various dysplasias found in these cases as well as in Recklinghausen's disease, in tuberose sclerosis and in syringomyelia, it would appear that in the future more attention should be given to dysontogenetic phenomena in persons who are suffering from glioma. Occasionally, dysplastic phenomena may also be found in the somas of the patients or of their ancestors. The significance of the relationship of these various genetic points of view in the clinical investigation of cases of tumor of the brain is obvious.

KESCHNER, New York.

ADDISON'S DISEASE. PAUL H. GUTTMAN, Arch. Path. **10**:895 (Dec.) 1930.

A statistical analysis is made of 566 cases of Addison's disease collected from the literature of 1900 to 1929, inclusive, and from the department of pathology of the University of Minnesota. The following points are emphasized: (1) the etiology and the classification of lesions in the suprarenal glands; (2) the pathologic anatomy of the lesions in the suprarenal glands; (3) the nature and significance of lesions elsewhere in the body, and (4) a correlation between the clinical manifestations of the disease and the changes in the suprarenal glands.

Contrary to the older views, Addison's disease does not occur without lesions in the suprarenal glands. In most cases both suprarenal glands are destroyed. A few cases of unilateral lesions are recorded. The pathologic changes, in the order of their frequency, are: bilateral tuberculosis, primary contracted suprarenal gland (atrophy), amyloid disease, neoplasms, vascular lesions, fatty degeneration and pyogenic infections. Syphilis and metastatic tumors of the suprarenal glands are rarely seen in association with Addison's disease. Many other lesions are described, such as atrophy due to pressure, hypoplasia, trauma, metaplasia of the bone marrow, etc.

The disease is relatively rare. Both sexes are affected. In the entire series, males are more frequently affected than females. In the cases of primary contraction of the suprarenal glands females predominate in the ratio of 1.6 to 1. Heredity can be considered a factor only in rare instances. The age incidence of primary contracted suprarenal gland and of suprarenal tuberculosis is approximately the same. In tuberculosis of the suprarenal glands, the age incidence follows closely that of deaths from tuberculosis in general.

Tuberculosis of the suprarenal glands is seldom seen in the absence of tuberculous lesions elsewhere in the body. The primary focus is usually in the lung, and ordinarily it is not recognizable clinically. Infection takes place through the blood stream. The medulla appears more susceptible than the cortex to the infection, and it is usually completely destroyed. Remains of the cortex can be made out microscopically in most cases. The disease is progressive and is characterized by periods of healing and periods of exacerbation. Healing is rarely observed.

Primary contraction of the suprarenal glands is a disease of unknown etiology. Two cases are presented which show an early and a late stage of the disease. The pathologic changes indicate that the condition is primarily a slow necrosis involving the cortical cells and leading finally to their disappearance. The inflammatory reaction is secondary to the degenerative changes. The degree of the inflammatory reaction depends on the severity and tempo of the degenerative changes. Partial function is maintained by regeneration in the form of small adenoma-like nodules of cortical cells. There is no evidence that the lesion is due to infection or to the toxic products of lesions elsewhere in the body.

The occurrence of thymic hyperplasia in association with Addison's disease is questionable. As far as could be determined, the weight of the thymus in cases of Addison's disease falls within normal limits. Changes in other glands of internal secretion are relatively rare. They cannot be considered of importance in the production of the symptoms of Addison's disease. Anatomic changes in the sympathetic ganglia of the celiac plexus are extremely few and variable. They are not considered of significance in the genesis of the symptoms of Addison's disease. Gastro-intestinal lesions in Addison's disease are infrequently observed. Peptic ulcers occur in only a few cases. They do not correspond in frequency with those that occur in animals in which the suprarenal glands have been excised. Bilateral tuberculosis of the suprarenal glands without symptoms of Addison's disease is not infrequent. These cases have been termed "latent tuberculosis of the suprarenal glands." Accessory cortical tissue and hyperplasia of the cortex of the suprarenal glands may prevent symptoms of Addison's disease in cases of destructive lesions in the suprarenal glands.

The duration of the disease is not affected by the presence of tuberculosis elsewhere in the body. The duration of the disease in primary contraction of the

suprarenal glands is longer than that in tuberculosis of the suprarenal glands; the mean for the former is 34.02 ± 4.40 months; for the latter, it is 13.15 ± 2.54 months.

The duration of the disease is significantly longer in cases in which pigmentation is the first and predominant symptom than in those in which pigmentation and weakness occur simultaneously and in those in which weakness is the initial and predominant symptom. It is suggested that pigmentation is a mechanism which is compensatory for the destruction of the suprarenal glands.

Conclusions as to the relative importance of the cortex and medulla cannot be drawn from a study of a single case or a small group of cases, as the symptoms of the disease are extremely variable. Evidence is lacking that the symptoms occurring in cases of primary contracted suprarenal glands differ from those occurring in tuberculosis of the suprarenal glands. No appreciable difference in the symptomatology can be noted with varying degrees of destruction of the cortex and the medulla. Available experimental and clinical evidence points to the fact that the adynamia, gastro-intestinal symptoms and low blood pressure are due to an accumulation of toxic substances subsequent to suprarenal destruction. The fatal result is due to cortical failure. All symptoms may be present in patients with an anatomically normal medulla; however, a functional disturbance of the medulla as the result of disturbance in synergism of the cortex and medulla cannot be denied.

WINKELMAN, Philadelphia.

THE ACUITY OF BINOCULAR DEPTH PERCEPTION IN HEMIANOPIA. E. V. L. BROWN and P. C. KRONFELD, Arch. Ophth. **4**:626 (Nov.) 1930.

The writers first discuss briefly but clearly the factors that enter into the various phenomena of binocular depth perception, that is, the peripheral as well as the central (cerebral) process. So far as the former is concerned, they acknowledge the work already done therein. The review of the central process is more extensive. In his theory of this process as presented in 1902, Verhoeff is quoted fully. He described the intermediate fibers or neurons on which the binocular perception of relief is dependent; he also called attention to the fact that this intermediate system may be regarded as the cerebral representative of the hypothetic cyclopean eye of Hering and of others. The work of Bárány and of Kleist is reviewed, as they discussed the anatomic representation or localization of ganglion cells wherein or whereby monocular images are formed. Other authorities are quoted as to the location of this cyclopean center. The authors briefly consider, as well, the probability that a fusion of horizontal disparity is separate from the processes of central calcarine fissure in the recognition of size, shape, form, space, etc. As they state, though, this factor does not interfere with the use of the term "central factor."

Heine's theory of the bicerebral representation of the macula is discussed. In view of the fact that he had based this theory on the presence or absence of binocular depth perception in cases of hemianopia, the authors express surprise over the neglect in the investigation of most important relevant factors, such as the intermediate processes, the conduction of impulses through the visual pathway and the primary reception of these impulses in the calcarine fissure. In comparison, active and extensive investigation had been carried out in this study of depth perception in anomalies of the peripheral receiving apparatus and in lesions of the terminal station of the brain.

In the discussion of Heine's theory, sketches are used to show the retinal incidence of the disparate images, the necessary association fibers that would coordinate these double images (one being conducted to each occipital lobe)—as the authors state it, the coordination of the cortical foveae—and the anatomic relationship of these association fibers as they lie in the visual pathway. They are either physiologically severed or allowed to remain intact by lesions that either destroy macular vision or spare the macula. This theory of Heine was supported by anatomic observations of Dejerine and Pfeiffer, and it is now known that these

association fibers exist. Based on this, patients with a hemianopia passing straight through the macula should have no central perception of relief, while patients in whom the macula is spared should have no disturbance of binocular vision. Heine had further decided that the size of this central portion of the visual field represented in both occipital lobes was approximately 8 degrees.

The apparatus used for testing is described. It followed closely that used and described by Howard in 1919 and now in use for the testing of aviation pilots. Six cases of homonymous hemianopia were selected, all with fields in which the macula was not spared. Cases of bitemporal hemianopia were rejected for certain proper reasons. In the procedure of fixation, careful attention was paid to mechanical assistance, so that a pseudosparing of the macula was eliminated. The normal ocular oscillations described by various investigators and quoted by the authors made this necessary. One case is reported in detail as an example (composite) of all the cases with the results obtained. The tests were done under different conditions, that is, with two different sizes of rod objects, with the rods separated on a horizontal level as well as with one above the other, with two different rates of shutter exposure and with two different distances between the observer and the rods. In addition, the tests were carried out at varying distances for the retinal incidence of the images from the actual point of fixation.

Before an interpretation of the observations is made, a brief discussion is given of the normal alternate fixation of these disparate rods and the impression of depth as it depends on the actual position of the testing rods and the horopter which is the locus for all subjectively equidistant points that could appear as the result of this alternate fixation. In this discussion the authors include the behavior of the hemianopic patient to certain factors that could be changed at will. Certain other theoretical probabilities are included, such as the influence of the homolateral eye, etc.

The authors' summary states that the values of the tests were within the limits allowed for the normal person, except that if the experiments were arranged so that one of the disparate images came to lie on a blind part and the other on a seeing part of the retinas, then the patient failed. This is in accord with Heine's theory. Further, the eccentric perception of depth in cases of hemianopia shows the influence of the curvature of the horopter and of the prevalence of the homolateral eye.

SPAETH, Philadelphia.

OXIDATIVE NATURE OF NERVOUS IMPULSE. EDITORIAL, J. A. M. A. **96**:865 (March 14) 1931.

A nerve deprived of oxygen rapidly loses its power to conduct the nervous impulse but soon regains it if oxygen is again supplied. It has been proved also that a nerve uses oxygen and gives off carbon dioxide during the passage of the nervous impulse and that this reaction liberates heat, which has been measured. Yet this does not prove necessarily that conduction of the nervous impulse is of an oxidative character, as waste products may be formed by the conduction, and these inhibit the process unless they are removed by oxygen.

After a nerve has been placed in an atmosphere of pure nitrogen, and oxygen is again admitted to the nerve chamber, there is an increased consumption of oxygen over the normal resting level, the increase being greater if the nerve is stimulated to activity during its stay in nitrogen. This demonstrates that a nerve is able to go into oxygen debt in the absence of oxygen, the debt being paid off when there is a supply of oxygen available. Under similar conditions, Schmitt (*Biochem. Ztschr.* **213**:443, 1929) has shown that extra carbon dioxide is not given off when a nerve is stimulated in nitrogen. Hence he assumed that conduction under anaerobic conditions may depend on the union of oxygen with some substance in the nerve, not necessarily a complete oxidation when the substance is oxidized to carbon dioxide. The only way that the nerve could obtain oxygen under anaerobic conditions would be from a molecule containing oxygen that was able to give up this oxygen readily when needed and later take up oxygen when it was again supplied to the nerve.

For several years, Warburg (*Science* **68**:437 [Nov. 9] 1928) has been studying the iron-containing respiratory ferments in tissues having the property of taking up molecular oxygen and of converting the oxygen into an active form that can be readily used by the tissues. Warburg has found that this reaction can be inhibited by carbon monoxide, and he believes that the carbon monoxide combines with the respiratory ferment in a manner similar to the combination of carbon monoxide with hemoglobin. If a tissue is placed in an atmosphere of carbon monoxide and oxygen, the respiratory ferment will combine with these gases in proportion to their partial pressures, so that, if the amount of carbon monoxide is increased and the oxygen decreased, practically all the respiratory ferment will combine with the carbon monoxide. Under these conditions, respiration will cease as the supply of oxygen activated by the ferment decreases.

Haldane showed that the ratio of hemoglobin combined with carbon monoxide to hemoglobin combined with oxygen can be altered by the action of light, which has the property of splitting up the carbon monoxide-hemoglobin compound into carbon monoxide and hemoglobin, thus diminishing this compound and increasing the amount of hemoglobin available for combination with oxygen. A similar reaction occurs with Warburg's respiratory ferment. Respiration of isolated cells may be decreased if carbon monoxide is added to the gases in the cell chamber in the dark; the carbon monoxide combines with the respiratory ferment. This inhibition of respiration will disappear when light is thrown on the cell suspension. Light causes the carbon monoxide combined with respiratory ferment to be replaced by oxygen, and respiration may proceed as the ferment again activates oxygen.

A similar mechanism of oxidation takes place in the nerve. Schmitt (*Am. J. Physiol.* **95**:650 [Dec.] 1930) tested the effect of mixtures of carbon monoxide and oxygen on resting nerves and found that respiration of carbon monoxide is decreased in the dark, but that, if the nerve chamber is illuminated, the usage of oxygen will be increased, similar to the change in respiration found by Warburg on cell suspensions. To corroborate this observation, Schmitt studied the effect of mixtures of carbon monoxide and oxygen on the action potentials of nerves. he found that in darkness the intensity of the action potential of a nerve can be reduced to zero in a mixture of carbon monoxide and oxygen, but that if light is thrown on the nerve, the action potentials will be restored to normal. If the nerve is placed in nitrogen and in darkness, the action potentials can be reduced to zero but cannot be restored by the action of light, thus showing that light has a specific effect on the respiratory ferment and not a general effect on the nerve.

From these experiments, Schmitt concludes that the action potentials in the nerve are primarily of an oxidative nature and that the oxygen used in the process requires activation by the respiratory ferment, which may be poisoned by carbon monoxide. It would seem plausible that the ferment simply provides the source of activated oxygen.

These experiments are interesting for the new clues which they provide with regard to the actual mechanisms that are involved in nerve conduction. They show, furthermore, a correlation between the oxidative processes in various types of cells.

EDITOR'S ABSTRACT.

THE INCREASING PREVALENCE OF PELLAGRA. EDITORIAL, J. A. M. A. **96**:614 (Feb. 21) 1931.

Recent reports by the U. S. Public Health Service indicate that the prevalence of pellagra has been increasing for several years in this country. The progress in the study of the disease, the newer insight into its probable etiology and the vaunted prophylactic as well as curative measures applicable to the malady have awakened the hope that uncertainty is about to be replaced by confidence in its management. Yet government records (Press Dispatches, Dec. 6, 1930) recently submitted to Congress contained the ominous information that the death rate from pellagra computed in 1924 as 2.5 in each hundred thousand of population rose steadily to 5.7 in 1928, and that in 1929 it was 5.5.

Pellagra is not a new disease, though its prevalence in the United States was not appreciated until the present century. In most countries it has been regarded as an essentially chronic malady confined almost entirely to the poorer classes in rural communities; but this has not been equally true in the United States, where it has been found to affect both the white and the Negro races. Pellagra was described nearly two centuries ago, as early as 1735, under the designation of mal de la rosa; but the present appellation (pelle agra, rough skin) dates from Francisco Frapolli's description in 1771. A hospital was early established in Milan for the treatment for the disease, a three-volume treatise, "De Pellagra," being published during the years 1786 to 1789 (Vanderhoof, Douglas: Pellagra, in Cecil: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1927).

Several theories regarding the cause of pellagra have been propounded. The oldest — the zeist hypothesis — attributed the disorder to the use of spoiled corn, as it occurred conspicuously among maize-eating groups. Subsequently, pellagra was classed by many in the category of infectious diseases due to a specific microorganism. There was much in its incidence to suggest a microbiotic etiology, but the latter has been abandoned largely because of the pioneer investigations of Goldberger and his associates in the Public Health Service. They have insisted on a dietary origin for pellagra, placing it in the category of so-called deficiency diseases. Pellagra does not occur in persons who regularly consume a well ordered mixed diet. The sufferers are likely to have subsisted on a regimen in which the protein content was low and of poor biologic quality, with a paucity of fruits and green vegetables. Goldberger believed that he had found an analogue of human pellagra in the so-called black tongue of dogs. This, like pellagra, yields to corrective dietary measures.

Recently, and again through Goldberger's leadership, attention has been called to the effect of vitamin deficiencies in provoking the appearance of pellagroid symptoms. The existence of a pellagra-preventing vitamin, designated successively as P-p B_2 and G according to current usage, has been postulated. This is part of the vitamin mixture formerly designated as water-soluble B. It has become possible to separate products such as yeast, rich in the vitamin B "complex," into parts, of which one is conspicuously antineuritic and another protective against a form of dermatitis that arises, in experimental animals, in its absence. Milk, meat and yeast are relatively rich in vitamin G, in which the cereal grains are poor. On such considerations, prophylactic measures have been based.

A somewhat different hypothesis has just been formulated by Bliss (Bliss, Sidney: Science **72**:577 [Dec. 5] 1930) at the Tulane University of Louisiana School of Medicine, who ventures the suggestion that pellagra is in reality an iron-deficiency disease. He points to anemia as a frequent concomitant of pellagra. He also notes that the foods which are supposed to contain liberal quantities of vitamin G (beef, liver, egg yolk, yeast) are all iron-containing foods (some of them being among those containing more iron than any other known biologic product), while the pellagra-producing diet of poor farmers of the South (molasses and corn bread) is extremely poor in iron. Bliss reports results of "a very encouraging nature" from iron therapy with pellagra patients. In severe cases the iron was administered intravenously, and in milder cases it was given orally. Experiments on animals also were encouraging. It would, of course, be extremely premature to endow these observations with the dignity of proof; many clinical students of pellagra still believe that the last word regarding the nature of the disorder has not been spoken. There are, indeed, reasons for assuming that pellagra as seen in man represents a syndrome — a group of symptoms including stomatologic, gastro-enteric, cutaneous and nervous manifestations, each of which may have independent pathogenic origin. The hypothesis of multiple deficiencies with consequent protean disease characteristics is somewhat appealing. It has again become "open season" in the hunt for explanations. The most recent morbidity statistics encourage vigorous pursuit.

EDITOR'S ABSTRACT.

MY DISCOVERY OF TWO NUCLEI OF THE HUMAN MIDBRAIN WITH ULTERIOR STUDIES ON THE OCULOMOTOR NUCLEI OF MAMMALIANS. CASIMIRO FRANK, Arch. gen. di neurol. e psichiat. **11**:1, 1930.

Nucleus intraconjunctivalis centralis, originally described by the author under the name of nucleus intracommissuralis wernekinckii (1919), and the nucleus subfascicularis are both located in the tegmentum of the midbrain. The first part of the paper consists of a polemic with Castaldi, the author defending his priority in the discovery and especially the novelty of the description of these two nuclei, which had been passed unnoticed by all previous students of this region. The nucleus intraconjunctivalis centralis must not be confounded with the part of the nucleus of the raphe mentioned by von Monakow under the name of "Fortsetzung des Raphekerns" (1909); on the other hand, the nucleus subfascicularis is not the formation described by Ziehen (1920) under the name of nucleus anuli FLP (i. e., fasciculus longitudinalis posterior) but an independent formation.

The second part of the paper deals with the author's research in comparative anatomy of the two nuclei mentioned and of the other formations of the tegmentum of the midbrain and the aqueduct (oculomotor nuclei, the central gray matter, the nucleus of Edinger-Westphal, the nucleus lateralis principalis, the fasciculus longitudinalis posterior, etc.). On the ground of these comparative anatomic studies, he draws some deductions as to the physiologic rôle of these formations. The nucleus intraconjunctivalis centralis exists in the cat, dog and cercopithecoid monkey (*Macacus*). It belongs to the system of the nucleus motorius tegmenti (Ziehen) and represents a relay station of the cerebellocerebral pathways. The author believes that functionally this nucleus contributes to the finer regulation of static and dynamic equilibrium as suggested by the fact of its great development in *Macacus*. This nucleus, together with the nucleus subfascicularis, participates also in the regulation of the function of sleep. The author refers the hypotonia as a component of the state of sleep to the pars dorsalis of the nucleus intraconjunctivalis centralis, while the ptosis (paralysis of the levator of the upper lid) is related to the pars lateralis of the nucleus subfascicularis. The latter nucleus exists in the cat, dog and *Macacus*. The present comparative anatomic studies tend to confirm a previously expressed hypothesis of the author that the lateral part of this nucleus represents an accessory nucleus for the antagonistic function of the levator of the upper lid and of the orbicular muscle of the eye. In the cat and in the dog, animals in which the palpebral function is little developed, this part of the nucleus subfascicularis is proportionately less developed as compared to *Macacus*, in which the palpebral function is almost as elaborate as in man. In both *Macacus* and man the pars lateralis of this nucleus has a distinct morphologic analogy, showing in both species the typical horseshoe shape, while in the cat and the dog it has an oval triangular shape. As to the medial part of the nucleus subfascicularis, this part probably represents the nucleus of the superior division of the facial nerve. This part of the nucleus subfascicularis is not well developed in the cat and the dog but, on the contrary, is highly developed in *Macacus*, in which the function of mimicry is almost as elaborate as in man. Following the same line of thought, the author is inclined to locate the center for the photopupillary reflex in the nucleus angustus parvicellularis of the so-called central gray matter. This nucleus is found only in mammals. On the contrary, the nucleus medianus anuli aqueductus is peculiar to man and is not found in other mammals; thus, the hypothesis of its being the center for the photopupillary reflex must be excluded. The nucleus medianus anterior, well developed in all mammals and in other vertebrates, probably represents the center for the primitive accommodation, while the synergic function of convergence and of accommodation (associated movements of two internal recti muscles and of sphincter iridis) has its center in the nucleus of Edinger-Westphal, which is different from the nucleus medianus anterior and is found only in mammals, being especially developed in those with binocular vision.

Plates with twelve colored photomicrographs of Nissl sections illustrate the paper. A summary in German is given at the end.

YAKOVLEV, Palmer, Mass.

AURICULAR TETANUS AND ITS RELATION TO OCULAR TETANUS. G. V. T. BORRIES, Rev. d'oto-neuro-opht. **8**:423 (June) 1930.

Auricular tetanus is not a particular disease, but the term applies to cases arising from the ear. While it is rare, it probably is more frequent than is supposed. Permin reported 371 cases of tetanus in Denmark, among which there was 1 case of auricular tetanus and none of ocular tetanus. The author was able to collect only 12 cases. One case occurred in a boy who was admitted to the hospital with the diagnosis of otitis with cerebral complication. Eight days before admission, a piece of wood had penetrated the left ear. The symptoms were pains in the ear and the back, trismus, convulsions and opisthotonos. The splinter was found in the ear, where it had caused injury of the anterior wall of the canal. Death occurred on the following day.

The symptoms of tetanus are not unlike cerebral complications of otitis; the stiffness of the neck suggests meningitis; torticollis is seen in tetanus and also in abscess of the neck of otogenous origin; Oppenheim has shown that trismus is found also in tuberculous meningitis affecting the two central gyri. The facial paresis characteristic of tetanus may also lead to an error in diagnosis. Other clinical peculiarities may make the diagnosis difficult; either an otogenous cerebral disease may exist with a picture of tetanus or an aural suppuration itself may cause tetanus. Moulonguet and Perrier observed a case of lateral sinus thrombophlebitis with trismus, contraction of the muscles of the neck and a positive Kernig sign in which tetanus was diagnosed and serum was given. After removing the thrombus, however, the patient recovered.

Auricular tetanus can appear without traumatism in a suppurating ear. Knud and Schroeder reported a case of prolonged otitis in which the tetanus was induced by scratching the canal with a hairpin. Meseck and Klestadt each reported a case of suppurating otitis complicated by tetanus in which a tampon of cotton soaked in pus, containing tetanus bacilli, was removed from the auditory canal. It is probably true that such an infection can arise in the cavity after a radical operation has been performed on the mastoid, although no case has as yet been observed.

Auricular tetanus occurs with the picture of cephalic tetanus, with trismus, dysphagia and at times a disease of the facial nerve, either a spasm or a paralysis. This latter may, however, be lacking and is certainly rarer in auricular than in ocular tetanus, which fact has some diagnostic importance. There seems to be no difference in principle between the manner in which the facial nerve and the other nerves are attacked in tetanus, but the facial nerve is perhaps more susceptible and its symptoms are more striking. In partial tetanus, the disease of the facial nerve may be either a paralysis or a spasm. In complete tetanus, the participation of the facial nerve is almost always in the form of a spasm. Other nerves may also be paralyzed in partial tetanus: the oculomotor, the trochlear, the hypoglossal and, perhaps, also the trigeminus. These local paralyses are easily overlooked because they are hidden by a spasm of the contiguous muscles. The same toxin can produce a spasm as well as a paralysis, and a single nerve can be particularly vulnerable.

A case is described in which the patient with facial paresis accompanying a suppurating ear was sent from the ophthalmologic to the neurologic clinic and from there to the otologic clinic. In the last, exenteration of the mastoid was done, and only later was it discovered that the case was tetanus from a previous lesion of the eye which had not been known.

In diseases of the facial nerve without apparent cause, tetanus must be thought of even if there is no history of traumatism. Likewise, when, after a traumatism of the ear or of the eye, a paralysis appears, it must be remembered that the latter is not always a consequence of trauma, but that it may also be a sign of tetanus.

DENNIS, Colorado Springs, Colo.

COMPLETE BILATERAL CONGENITAL EXTERIOR OPHTHALMOPLEGIA AND DOUBLE PTOSIS. G. E. DE SCHWEINITZ, Arch. Ophth. **5**:15 (Jan.) 1931.

This article is a clinical communication covering, in great detail, the history, general examination, neurologic examination, ocular and special examinations and the course in a case of bilateral congenital exterior ophthalmoplegia, due, apparently, to bilateral cortical atrophy of the frontal and parietal regions. The etiologic factor as given, i. e., bilateral cortical atrophy, was based on encephalograms (illustrated in the article), which revealed enlargement of the subarachnoid spaces. This was regarded as evidence of atrophy of the brain in the frontoparietal area. There was an absence of an appreciation of touch, pain, heat and cold over the left hand and arm to the elbow, over the right hand and arm to the shoulder, over both legs to Poupart's ligament, over the entire forehead and face to the mandible and over an irregular area in the back of the neck. The sense of smell was faulty. The patient had an attack of unconsciousness while in the hospital and gave a history of other similar attacks. Relative to these symptoms, Dr. Spiller stated that hysteria might play a large rôle in the symptoms of this patient. The author states that the sensory condition cannot be explained on an organic basis, and there was certainly enough in the patient's history for the probability of hysteria in association with organic disease. The visual fields showed an almost complete absence of the nasal fields and considerable contraction of the preserved areas, greater in the left field, suggesting somewhat an impure binasal hemianopia.

Following the report of the case there is extensive comment on congenital ophthalmoplegia and double ptosis, with mention of the various authorities and the symptomatology of this condition. The pathologic histology as discussed by Bearing, Moebius, Oppenheim, Gowers, Huebner, Heuck, Axenfeld, Bradburne, Lawford, Carey and Li and as reviewed by Langdon and Cadwalader is outlined. The encephalographic studies are apparently the first ever made in a case of congenital external ophthalmoplegia. The diagnosis of bilateral cortical atrophy of the frontal and parietal region seemed to be authoritative, in that it was given by Dr. H. K. Pancoast, confirmed by Dr. Pendergrass and further discussed by Dr. Temple Fay. Dr. Fay's interpretation of the encephalograms included not only frontoparietal atrophy, but also pressure on the chiasma. In such a circumstance, the ophthalmoscope should reveal atrophy of the optic nerve. However, the optic disks in this patient were entirely normal.

The article closes with a brief discussion of the "hysterical" manifestations in this case and their control. The etiologic factor is abstracted very well by the statement that, "the patient's ophthalmoplegia is best explained by assuming the combined influence of nuclear aplasis or dysplasis associated with imperfect development and structural defects of the exterior ocular muscles."

SPAETH, Philadelphia.

ON THE SURVIVAL OF THE MATERNAL IMPULSE IN AGED DEMENTED VIRGINS. J. NARDI, Arch. gen. di neurol. e psichiat. **11**:140, 1930.

Among the primordial instincts, from the philogenetic standpoint the maternal instinct is the most conspicuous. In a crude, unconscious form, this instinct is evident in invertebrate animals; as it develops along the scale of evolution from the simpler organisms up to man, it becomes one of the most complex reactions. While at first it is a purely sensorimotor phenomenon, eventually it becomes a psychosensory manifestation. Since the maternal instinct is one of the earliest forms of nervous activity, it may survive even after the higher intellectual faculties are destroyed. The author reports three interesting observations of aged, demented virgins in whom the most genuine manifestations of the maternal instinct appeared under appropriate stimulation in spite of the advanced dementia. In relationship to the degree of mental deterioration, each patient showed various degrees of preservation of the maternal instinct. The first patient, a virgin, aged 72, with complete extinction of affect, indifferent to her own family and to surrounding persons, confused and incoherent, became attached to a feebleminded child, was

solicitous of its welfare, surrounding it with marks of a most genuine motherly affection. These manifestations of maternal instinct persisted even when the child was away from her. In the second patient, a virgin, aged 62, in a state of profound dementia, the manifestations of maternal instinct emerged when an idiotic girl, aged 9, happened to be placed in her immediate surroundings. Whenever the patient saw this girl, she petted and caressed her, assisted her at feeding, and wiped her nose and mouth, while mumbling incomprehensible words in a most affectionate tone. The patient showed these maternal manifestations, however, only in the immediate presence of the child; when the girl was taken away for several days the patient would be completely indifferent until the child returned. In the third patient, a virgin, aged 59, who had been in a state of complete dementia for many years, the manifestations of the maternal impulse (caressing, petting) were observed whenever the patient was in the presence of children; in this case no preference was shown for any particular child. The author points to the regression of the maternal instinct in relation to the dementia from a relatively high psychosensory form of expression (case 1) to a lower form in which the maternal instinct manifested itself only under direct stimulus (the presence of the child, case 2), and finally, to the lowest form of a crude, instinctive impulse, a sort of exclusively sensorimotor reaction without conscious purpose or any psychoeffective content (case 3). The author discusses the neurobiologic aspects of the maternal instinct and believes it to be, together with other fundamental instincts, a function inherent to the cerebrum. Though regulated (activated) by various physiologic factors (hormonal), the maternal instinct is not created by these factors but is an innate function of the nervous system.

YAKOVLEV, Palmer, Mass.

MICROGLIA AND OLIGODENDROGLIA: I. METHODS OF IMPREGNATION. D. BOLSI, Riv. di pat. nerv. **36**:60 (July-Aug.) 1930.

The author proposes a method for impregnating microglia and oligodendroglia. The tissue is fixed in a mixture of formaldehyde and bromide for from twenty-four to forty-eight hours. From this fixative the tissue is passed into a solution composed of: pyridine and acetone in equal parts, 5 cc.; commercial formaldehyde, 15 cc.; distilled water, 75 cc.; ammonium bromide, 3 Gm. In this solution it may be kept for several months.

In the second step of the technic, the blocks are washed in distilled water and frozen sections, 15 microns thick, are cut. The sections are placed in distilled water and then passed into a 20 cc. solution of the mixture of ammonium bromide, pyridine, acetone and formaldehyde which has been described. The temperature of the fluid is slowly raised to between 45 and 50 C., and the fluid is then left to cool, after which the sections are transferred to distilled water. The whole procedure takes about ten minutes.

The sections are then transferred for at least five minutes into 20 cc. of the following solution, which must be kept in a tightly closed bottle: distilled water, 160 cc.; glycerine, 40 cc.; concentrated ammonia, 100 drops. It is advisable to stir the sections occasionally. Without further washing, the sections are then transferred to 20 cc. of a 2 per cent solution of silver nitrate in which they are left from forty to sixty seconds. The silver solution should be changed frequently. Without washing, the sections are then transferred to 20 cc. of a 2 per cent solution of commercial formaldehyde, to each 100 cc. of which 5 cc. of gum arabic is added. The sections are left in this for about five minutes. This reducing solution must also be changed frequently. The sections are then washed in distilled water. The sections may then be transferred to a 2 per cent solution of yellow gold chloride, 2 per mil., and following rapid washing in distilled water they are transferred to a 5 per cent solution of sodium hyposulphite dissolved in 50 per cent alcohol. A fresh washing follows.

The sections are finally transferred to 70 per cent and then 95 per cent alcohol, and carbolxylene (3 parts of xylene to 1 part of crystallized carbolic acid) and mounted in balsam.

CELL TYPES IN THE GLIOMAS: THEIR RELATIONSHIP TO NORMAL NEUROHISTOGENESIS. CYRIL B. COURVILLE, Arch. Path. **10**:649 (Nov.) 1930.

Based on the study of the cell types in a series of fifty gliomas, a classification is suggested that is grounded on the course of development of the constituent cells: Group 1, gliomas in which the cellular arrangement is, to a greater or less degree, suggestive of that of the primitive neuro-epithelium; in some instances it is probable that some of the cells are capable of differentiating into neuroblasts and glioblasts. Group 2, gliomas arising from embryonic or adult ependymal tissue, growing into the ventricular system instead of the brain substance. Group 3, gliomas apparently arising from cells that have migrated from the environs of the neural cavity. The mother cell of such gliomas resembles the migrating undifferentiated cells of the pallium and, like them, is bipotential, capable of forming glioblasts or neuroblasts. The malignancy of the various types depends on the degree of cellular differentiation. Group 4, gliomas that develop in consequence of the division of fully developed cells, usually of glial type; fully matured ganglion cells are probably not capable of neoplastic proliferation. Group 5, tumors arising from the appendages of the brain, the pineal and the pituitary glands.

In the embryonal gliomas, the differentiation of the various elements is compared to stages in normal neurohistogenesis as it is now understood. The histologic aspects of the tumor are dependent on the stage reached in the histogenesis of the fundamental cell and the location of the hypothetic "mother cell" when it assumed neoplastic activity. Regressive changes may also alter the primary appearance of the tumor.

The embryonal gliomas seem to be composed of undifferentiated cells that are bipotential, being capable of forming either glioblasts or neuroblasts. Such cells pass through various stages suggestive of normal neurohistogenesis.

WINKELMAN, Philadelphia.

MICROGLIA AND OLIGODENDROGLIA: II. COMPOUND GRANULAR CORPUSCLES. D. BOLSI, Riv. di pat. nerv. **36**:74 (July-Aug.) 1930.

Using his own method, the author studied the origin of compound granular corpuscles. While some authors believe that compound granular corpuscles originate exclusively from microglial elements, others, among whom are Ferraro, Davidoff, Scheffer, Meduna, Pruijs, Jakob, DeRobertis and Daddi, believe that the oligodendroglia participates in the formation of such elements. From his investigations, Bolsi concludes that in the process of repair in experimental lesions of the central nervous system, the majority of the compound granular corpuscles are derived from microglia cells, although some cells of the vascular adventitia and of the connective tissue of the meninges contribute to their formation. Little is contributed by the elements of the blood and nothing by the vascular endothelium. Bolsi denies that oligodendroglia is transformed into compound granular corpuscles. He claims that oligodendroglia cells hardly react to destructive processes and that the reaction is of a degenerative type. In this respect oligodendroglia is in contrast with the astrocytes as to their lack of progressive changes. Bolsi denies also the degenerative significance of the microglial reaction which has been brought forth by Belloni.

FERRARO, New York.

CATATONIC NARCISSISM IN SCHIZOPHRENIA AND ITS EXTREME EXPRESSION IN THE EMBRYONAL BODY ATTITUDE. M. LEVI BIANCHINI, Arch. gen. di neurol. e psichiat. **11**:43, 1930.

The material for this "essay of psychoanalytic interpretation of schizophrenic catatonia," as specified in the subtitle of the paper, was offered by the observation of a schizophrenic patient, aged 31, who for many years was in a pronounced state of catatonia, and in whom there eventually developed a tonic rigidity with contracture in flexion of the head, trunk and extremities, in which position he

remained for four years until death. The author points out that the anatomico-physiologic approach in the interpretation of this variety of catatonic syndrome is possible and refers to the work of Pinto Cesar, Orton and Claude. However, the cause and the mechanism of this extreme flexion attitude of body may be entirely psychogenic. It is the latter hypothesis which the author defends as probable and plausible. He insists that the catatonic rigidity, in its more complete form, is an exquisite expression of negativism. It is an error to regard the latter as a passive and purely automatic phenomenon. In the author's point of view, catatonic patients maintain a vigilant and precise psychic activity, "full of ideas and representations"; however, this psychic activity is "polarized" around one dominant ideo-affective complex. Catatonic rigidity is an active defense reaction against all external influences tending to modify the position of the body assumed by the patient under the influence of definite, though unconscious, motives. The author regards the catatonic state as the function of an extreme degree of narcissism, or total transformation and interiorization of the object-libido into the ego-libido. Catatonic narcissism is a grave symptom of schizophrenia, especially when it acquires the expression of an embryonal body attitude. The latter might be regarded as an unconscious symbolization of the supreme wish never to have been born and to remain eternally in the bosom of the mother — the earth.

YAKOVLEV, Palmer, Mass.

DIABETES INSIPIDUS. C. RIZZO, Riv. di neurol. **3**:540 (Nov.) 1930.

In a case of diabetes insipidus, the author established a deficiency of chlorides in the blood and urine; increase of the potassium content of the blood; a slight edematous condition of the skin; increased hydrosaline diuresis and a low specific gravity; a low acidity, which was easily modified by food or by sodium bicarbonate; a modified acid-base equilibrium with signs of acidosis; a tendency to the rapid elimination of sodium chloride, and other signs of dissociation between hydric and solid diuresis. It was, therefore, a case with hypochloremia and normal hypochloruria that did not fit in the schemes of Viel and in which the metabolic disorders, probably secondary to a condition of acidosis, might have involved either the renal apparatus or the tissues in general.

The most constant phenomenon was the fixed quantity of hydric diuresis, which was independent from a suppression or an increase in the ingestion of water. With the dilution test, the author showed that an increase of water above the average amount used by the patient did not cause an increase in diuresis, but resulted in its progressive reduction. The author suggests that this phenomenon should be studied in other cases of diabetes insipidus in order to establish the connection with a possible modification of the acidity of the tissues.

From a pathogenic point of view, the author stresses the importance of the diencephalic region on the basis of the clinical peculiarities and of an x-ray investigation of the patient. Lesions, possibly inflammatory, due to propagation from a hyperplastic sinusitis, must have involved both the endocrine and nervous component of the hypophysis-diencephalic region, thus giving rise to the diabetes insipidus. It is probable that the inflammatory process might have involved primarily, and possibly more seriously, the pituitary gland and only secondarily the diencephalic area.

FERRARO, New York.

THE PERMEABILITY OF THE CAPILLARIES OF THE SKIN IN NERVOUS DISEASES. M. CHASANOW, Monatschr. f. Psychiat. u. Neurol. **75**:62 (Feb.) 1930.

The permeability of the capillaries of the skin was investigated in 125 patients with various diseases of the nervous system. The method used consisted in the application of a cantharides plaster to the flexor surface of the forearm. The albumin content of the blister formed in this manner was compared to the serum albumin, thus giving an index of the capillary permeability. The period of time

required for the production of the blister was also noted. Shorter and longer periods than normal were regarded as signs of increased parasympathetic and sympathetic activity, respectively. As a rule the capillary permeability was increased in patients with epidemic encephalitis, multiple sclerosis, acute inflammatory conditions and acute stages of vascular diseases, as well as in those with some endocrine disturbances and trophoneuroses. During chronic stages of syphilitic, circulatory and polyneuritic disorders, the capillary permeability was normal or decreased; similar observations were made in patients with gliosis, epilepsy and tumors of the brain and spinal cord. Extrapyramidal conditions that were not due to epidemic encephalitis also showed normal or decreased values. The formation of blisters was delayed in practically all conditions except exophthalmic goiter and sensory and trophic disorders of a peripheral nature, in which the reaction time was shortened. In patients with epidemic encephalitis there was some parallelism between the permeability of the blood-cerebrospinal fluid barrier for bromide and the capillary permeability for albumin, the latter being increased and the former decreased in eleven of twenty cases. In three cases, normal figures were obtained for both substances. The lipase content of the blood serum was decreased in a number of cases showing an increased capillary permeability.

ROTHSCHILD, Foxborough, Mass.

EXPERIMENTAL RESEARCHES ON MICROGLIA. C. I. URECHIA and MIHALESCU, Arch. gen. di neurol. e psichiat. **11**:95, 1930.

After a brief review of the researches into the function and reactions of microglia and oligodendroglia in various pathologic conditions, the authors point out the uncertain and contradictory results so far obtained. They report a series of sixteen pathologic protocols of their experiments, mostly on rabbits. They produced lesions by anemia, congestion, hypothermia, by injection of toxic substances into the brain, by introduction of foreign bodies (laminaries, stones, etc.) and by caustic and necrosis-causing substances. The animals were killed after various intervals of time, and sections of the nerve tissue were stained according to Hortega's method, with the addition of fat stains in a few instances. Around foreign bodies, in the nodules of necrosis and in the foci of inflammation, the Hortega cells play an important rôle. One finds a great number of cells filled with fat and there are also so-called areolated cells forming a red crown (Scharlach) and showing an active phagocytosis. Such cells are found as early as two days after the lesion; only a few are present twenty-four hours after the lesion, but they may be found even as late as twenty days after the lesion. The cerebral tissue reacts against the foreign body and against irritation or necrosis by the formation of a first layer of proliferative tissue, consisting mainly of lymphatic cells and of a few microglia cells, then by the formation of the second layer of microglia and of the areolated cells, and last by the third layer of dense gliosis. The scar is supported by profuse connective tissue. The two types of microglia cells react in a somewhat different way; Hortega cells are much more mobile and active, while the reaction of oligodendroglia is less evident. The authors have observed only direct mitosis of the Hortega cells; their transformation into areolated cells was obvious. Nine photomicrographs illustrate the paper.

YAKOVLEV, Palmer, Mass.

CROSSED APHASIA? L. DE LISI, Riv. di pat. nerv. **36**:4 (July-Aug.) 1930.

The author reviews all the cases in the literature in which aphasia was associated with left hemiplegia in right-handed people and cases of aphasia occurring in left-handed people with lesions in the left hemispheres. De Lisi's review concludes with the statement that, except for one case reported by Mendel, all the cases lacked a complete histologic study. The author adds to the literature the report of one of his own cases in a left-handed woman, aged 72, who, following ictus, presented a left hemiplegia and motor aphasia. At autopsy, macroscopic

examination of the brain revealed large areas of softening of the right hemisphere involving the two posterior thirds of the first parietal convolution and caudally to the second occipital convolution. From the clinical data and from the macroscopic examination, one might have concluded that the motor aphasia was the result of the involvement of the right hemisphere. However, serial sections of the whole brain with the Weigert method disclosed a small area of softening in the left hemisphere involving the white substance of the second and third frontal convolutions and part of the supralenticular area. These lesions had escaped detection under gross macroscopic examination; their location and extent are more than sufficient to explain a common type of motor aphasia. From this case and others reported in the literature, de Lisi reaches the conclusion that no sure proof exists as to the possibility that in some persons a complete transposition may occur of the centers of speech from the left to the right hemisphere, and that from a general point of view, considering the doubtful data on which its occurrence has been established, the participation of the right hemisphere in the adult in the function of speech must also be considered doubtful.

FERRARO, New York.

ACCOMMODATION. ALEXANDER DUANE, Arch. Ophth. **5**:1 (Jan.) 1931.

This posthumous article, presented through the courtesy of the widow of Dr. Alexander Duane, is a chapter from the uncompleted book on "Ocular Muscles" on which he was working at the time of his death. The difficulties in the Helmholtz theory of accommodation and other hypotheses relative to accommodation, i. e., those of Tscherning, Stilling and Lindsay Johnson, are considered in their disagreement with the original Helmholtz theory. Some varied experimental work is described in sufficient detail. The relationship between presbyopia and accommodation is considered. As Duane states, the phenomena of presbyopia are much more easy to understand if one admits that accommodation is effected not by a passive dilatation of the lens due to the elasticity of its capsule, but by a direct stress applied to the lens from without. For then, any increase in the resistance of the lens would create opposition to the external stress and thus would interfere with the lenticular expansion. A further possibility is that progressive diminution in accommodation is due in part to progressive diminution in the power of the ciliary muscle. This possibility is properly considered in great detail, being in the reviewer's opinion probably a most important factor.

In the author's conclusions, he states rather definitely that while the evidence of physiologic optics is strongly in favor of the Helmholtz theory, the evidence of physiology and anatomy and of clinical observations seem to point rather to one of the theories which ascribes the lenticular expansion occurring in accommodation to force applied directly to the lens.

SPAETH, Philadelphia.

THE HYPOPHYSEAL HORMONE. J. WATRIN, Rev. franç. d'endocrinol. **8**:193 (June) 1930.

After an interesting and rather complete review of the literature on the influence of the pituitary gland on sexual activity, the author cites the results of his own research, using guinea-pigs as laboratory animals. Gland tissues freshly prepared were used. It was found that the hypophyses of old females incapable of reproduction caused no genital reaction. The hypophysis of a sheep was not particularly potent, and the commercial extracts gave only negative results. However, tissue from an adult guinea-pig in full sexual activity, implanted in a guinea-pig at puberty, produced a distinct genital reaction within five days after the implantation. Apparently the graafian follicles were particularly affected for many became mature. Further implantation caused a rupture of the graafian follicles and their transformation into corpus luteum. A definite uterine change, which is supposed to depend on the ovarian reaction, was also noted. The author concludes from his research that the hypophysis exerts a strong influence on the ovary, which is apparently

very sensitive to the hypophyseal hormone. It likewise appears to have some influence in the development of the male genital glands, particularly the interstitial cells. Also it was noted in those animals in which an implantation of the pituitary had been made that there was an increased activity of the thyroid and of the pituitary glands; this was shown macroscopically by an increase in volume and a congestion, and microscopically by an increase in the size of the thyroid cells and by an increased flow of blood in the gland.

WAGGONER, Ann Arbor.

ANATOMICOTOPOGRAPHIC AND MICROSCOPIC RESEARCHES ON THE LYMPHATIC VESSELS OF NERVES. ALDO DEFRISE, Arch. gen. di neurol. e psichiat. **11**:102, 1930.

Defrise studied the question whether the intra-arachnoidal space or, as he prefers to say, the cleft of the arachnoidal connective tissue communicates directly with the lymphatic system; in other words, whether the cerebrospinal fluid does or does not reach the peripheral lymph nodes. Following injections into the nerves (median, crural, sciatic, perineal and posterior tibial) of new-born infants and of dogs, he came to the following conclusion: The lymphatic vessels of nerves originate in a closed system of the interfascicular reticulum not connected with the interlamellar spaces of the perineurium. Thus, these spaces must not be considered as lymphatic spaces. The perineurium represents a sort of membrane of separation between the endoneural medium directly communicating with the interstitial spaces of the arachnoid bathed by cerebrospinal fluid and having no lymphatic vessels, and the epineural or interfascicular medium provided with a lymphatic reticulum and carrying both the histolymph and the cerebrospinal fluid filtered through the perineurium. The efferent lymphatic vessels of the epineurium, after a short course, open into deep lymphatic channels and follow the latter's destination. There are no long collectors of lymph which, following the epineurium, would joint distant lymph nodes. The fluid (china ink) injected into the perineurium penetrates to the periphery of the nerve through the most minute lymphatic ramifications and eventually becomes diffused in the perimysium of the muscles. From this point, the lymphatic vessels of the muscles, emerging at the so-called neurovascular area (hilus of the muscle), reenter the system of deep lymphatics.

YAKOVLEV, Palmer, Mass.

XANTHOMATOSIS OR LIPOID HISTIOCYTOSIS. P. HEATH, Arch. Ophth. **5**:29 (Jan.) 1931.

This paper is divided into two parts: (1) a report of ocular observations in a disease known as Christian's syndrome, and (2) suggested new classifications of syndromes that are apparently related. The cases belong to a group showing defects of the bones of the skull, exophthalmos and diabetes insipidus. The two cases on which the article is based are described in detail. The exophthalmos and its mechanism in this group are of prime interest, and the author considers that the exophthalmos is produced by pressure and the loss of bony support at the apex of the orbit. Probably these ocular signs and the other signs that have appeared develop from a metabolic disease. The basis for this view is the necropsy material from one case. The patient in the second case recovered from the disease to a large degree. Photographs, photomicrographs and roentgenograms illustrate the article.

The suggested classification of related syndromes covers the correlation of Gaucher's disease, Niemann-Pick's disease, Christian's syndrome, Tay-Sachs' disease, Coat's disease and von Hippel's disease. Considering the experimental work that has been done on these diseases, the ophthalmologist has contributed important aid toward attempting the solution of a relationship. As the author states, "the whole range of liporeticular disease constitutes a medical play in which one character may wear many masks or assume many rôles." He was speaking of the etiology. There are certainly many similarities and constitutional and familial tendencies in the group considered.

SPAETH, Philadelphia.

A Physiologic Sketch of Attention. Jean Wintsch, Schweiz. Arch. f. Neurol. u. Psychiat. **26**:209, 1930.

The author cites a few incidents which show the unreliability of even intelligent persons as witnesses of unexpected occurrences. In previous tests of visual and auditory attention conducted among students 15 years of age, Wintsch found that while the average scores of the different classes to which these students belonged corresponded to their respective scholastic ranking, this was by no means true so far as the individual students were concerned; for instance, a student at the head of his class might not do as well as one at the foot. It was further found that performance in tests of visual attention was not necessarily proportional to that in tests of auditory attention. The author concludes, therefore, that attention as an entity does not exist, that it varies with each form of sensation and almost with each person, being determined by the individual's special interests and his affective states.

In this paper the author records the results of rather ingenious tests of visual attention, the observations being in essential agreement with those obtained previously. It is further shown that the individual's performances in different tests in this one type of attention vary, no one doing equally badly or equally well in all tests. Scores of an individual's successive trials in a given test indicate a preliminary period of adaptation followed by one of optimum performance and finally by one of fatigue. The author draws an analogy between his work and that of Pawlow on the conditioned reflexes and discusses the various factors which influence attention. In conclusion, he suggests the application of such studies in the field of education.

Daniels, Rochester, Minn.

Microglia and Oligodendroglia in Experimental Intoxication and in Postmortem Changes. F. Vizioli, Riv. di neurol. **2**:365 (Oct.) 1929.

The author studied the microglia and oligodendroglia following experimental lead poisoning by the use of hypodermic injections of lead acetate in 1 per cent solution. Some of the rabbits used were killed ten or fifteen days after the beginning of the experiment, while others were kept alive for almost a month and a few as long as one and one-half months. He has not been able to secure good impregnation of the microglia, which is easily accomplished in normal animals; this failure may be related to physicochemical changes due to the presence of lead.

Among the changes described is the acute swelling of the oligodendroglia of Penfield and Cone. The author emphasizes that the microglia may also participate in this process of acute swelling. In periods of more advanced intoxication the microglia undergoes degenerative changes that consist of shrinkage and breaking down of the processes. In a very few instances attempts at progressive changes were observed.

In another series of experiments the author studied the postmortem changes of the same elements and found many resemblances between the changes occurring in postmortem autolysis and those in experimental lead poisoning. He advances as a hypothesis the statement that toxic changes in oligodendroglia and microglia may be interpreted as phenomena of autolysis which have already taken place intra vitam.

Ferraro, New York.

The Differentiation of the Ocular Manifestations of Hysteria and of Ocular Malingering. E. B. Spaeth, Arch. Ophth. **4**:911 (Dec.) 1930.

In this review the essayist first describes the psychiatric side of hysteria as well as of simulation. The various types of simulators are divided into three general classes: the malingerer of normal mentality, the degenerate malingerer and the psychopathic malingerer. Posttraumatic relationships to malingering are also considered. The differentiation from the standpoint of the general symptomatology of hysteria and of malingering is considered. By a comparison of the

ocular symptoms in these two conditions, a differentiation between them is carried through the various possible symptoms that appear. The important ophthalmologic symptoms include: sensation, corneal and cutaneous; lesions of the skin and conjunctivae; vision, central and paracentral; visual fields; oculomotor disturbances, strabismus, diplopia or polyopia, nystagmus, ptosis and blepharospasm; mydriasis, miosis and cycloplegia; light and color sense; asthenopia, vertigo and dizziness. All of these symptoms are compared in some detail. Tests for the detection of simulation or for the diagnosis of hysteria are not included. They would be irrelevant in this review. Further, the author expresses a word of warning as to the value of the tests, in that so often they have the element of pain, surprise and of "trapping" the patient. In many instances the patient with true hysteria responds to these tests in the same manner as the simulator. A bibliography on the subject closes the article.

SPAETH, Philadelphia.

DOES EXTROVERSION-INTROVERSION OFFER A CLUE FOR PROGNOSIS AND TREATMENT OF PROBLEM BOYS? THEODORE NEWCOMB, Ment. Hyg. **14**:919 (Oct.) 1930.

Reasoning *a priori*, one might assume that the extrovert, having outwardly directed interests, would respond more hopefully to therapy aimed at social adjustment than the introvert, who naturally would be less susceptible to influence from the outside. To test the truth of this, Newcomb studied fifty-one boys at a Child Guidance Camp. He asked the counselors to record the responses to significant situations as they arose. When Newcomb analyzed the results, he found that responses in the same boy to similar situations varied between those labeled introvert and those labeled extrovert, and that all the boys combined tendencies toward introvert behavior with tendencies toward extrovert behavior. Yet most of these boys came to the camp with a record that indicated a decided bias to one psychologic type or the other. This, Newcomb believed, was evidence that the raters had the habit of logical association, and, having once classified a boy, they saw only the qualities that fitted that type. While he does not dare say that the type distinction has no real existence, he does emphasize the possibility that introvert-extrovert distinction may represent a psychologic presupposition rather than an objectively observed behavior distinction.

DAVIDSON, Newark, N. J.

HOMOGRAFTS OF TUMORS IN THE BRAIN. C. GUERRIERO and L. ZAGNI, Riv. di neurol. **3**:327 (July) 1930.

The purpose of the work was to investigate the statement that brain tissue offers a particularly favorable ground for the proliferation of neoplasms. The authors worked with three different types of tumors which they grafted into the brains of rats: the sarcoma of Jensen, the melanosarcoma of the rat and the adenocarcinoma of the rat. The tumor to be grafted was finely ground and introduced by means of a syringe into the brain tissue of rats. As a control, the material of the tumor was at the same time introduced into the subcutaneous tissue of the same animal.

From the results of the experiments, the authors conclude that intracerebral homografting of the tumors mentioned gave a percentage of positive results considerably lower than that following subcutaneous grafting. The development of the tumors grafted in the brain was much slower than that of the tumor grafted into the subcutaneous tissues; in the same length of time, the volume of tumor developed in subcutaneous tissue is five or six times larger than that developed in brain tissue. The authors therefore do not believe that the cerebral tissue constitutes a particularly favorable ground for the proliferation of neoplastic material.

FERRARO, New York.

CHRONIC RETROBULBAR NEURITIS. W. H. WILMER, Arch. Ophth. **4**:817 (Dec.) 1930.

This article, read at the hundredth anniversary of the Tennessee State Medical Society, discusses eight cases of retrobulbar neuritis in its chronic form only. In this discussion, the papillomacular fibers alone were covered. There is a brief discussion on the anatomy of the optic nerve. The series of eight cases is then presented to illustrate retrobulbar neuritis, unilateral and bilateral, from the standpoint of the various etiologic factors that were present, i. e., from disease of the gallbladder with tuberculosis, from sinus infection, probably from the teeth, tonsils and sinuses and from probable disseminated sclerosis and Leber's disease. The reports are illustrated with charts of the visual fields and a familial chart in the instance of a case of Leber's disease, and the cases themselves are related in detail from a clinical standpoint. The changes in the visual fields are emphasized, and the histopathologic changes in the optic nerve are given in detail.

The conclusions emphasize the importance of a detailed family history, the colloid curve of the spinal fluid indicative of disseminated sclerosis, the possibility of disease of the pituitary body, the absolute necessity for painstaking perimetric measurements and the relationship of disseminated sclerosis and Leber's disease in retrobulbar neuritis. The article closes with a brief résumé of the possible therapeutic measures.

SPAETH, Philadelphia.

SYMPATHECTOMY BY ARTERIAL EXCISION. EDWIN P. LEHMAN, Arch. Surg. **21**:838 (Nov.) 1930.

Excision of a section of a whole vessel includes removal of its adventitia and is, therefore, a form of sympathectomy. Lehman suggests that in cases in which an artery is permanently occluded this procedure will be simpler than stripping the adventitia, and, he believes, as effective. He illustrates this by the presentation of eight cases. In one, a calcified artery was injured accidentally in an intended sympathectomy, and the patient showed general trophic improvement following removal of the injured segment of the vessel. In another patient gangrene was threatened from a thrombosis in the femoral artery following a bullet wound; in this case cyanosis was lessened and the area of skin was improved following arteriectomy, although ultimately the patient died. In a third case an embolus rendered a femoral vessel useless and removal of 2 inches of this artery resulted in a definite but temporary improvement in circulation to the limb. Gangrene eventually resulted. Two cases of thrombo-angiitis obliterans were presented, and in each temporary relief was afforded, but in neither case was the limb saved from amputation. There were also three cases of arteriectomy for traumatic aneurysm, with good results. Lehman's conclusion is that arterial excision is indicated to improve circulation only when the vessel is permanently occluded, and he warns against following this procedure when there is any question about the usefulness of the vessel involved or the adequacy of the collateral circulation.

DAVIDSON, Newark, N. J.

A SYMPTOM OF FACIAL PARALYSIS. R. WARTENBERG, Klin. Wchnschr. **9**:1587 (Aug. 23) 1930.

If, in a normal person, one tries to press down the closed upper eyelids by means of the fleshy part of the thumb, against the resistance of the subject, one can feel the fine vibration of the orbicularis oculi. One can recognize that the definite contraction of the muscle is made up of a total of very fine contractions. In neuropathic persons this vibration is pronounced. In a complete and recent peripheral facial paralysis, this objectively palpable vibration in the orbicularis oculi is entirely absent in passive lifting of the upper lid. As the paralysis diminishes, this sign gradually sets in with increasing strength, but it always remains weaker than the vibration on the healthy side. It takes a long time to return to normal.

The diagnostic significance of this symptom is in the fact that it can be found either alone or in conjunction with other signs (paresis, associated movements, contractures, weakening of nasopalpebral reflexes) in an old facial paralysis and can indicate the degree of restitution in such a paralysis. The symptom is found definitely in old cases of facial paralysis of even twenty-two years' duration in which function is almost completely restored. The sign may also be the first to indicate a facial involvement in a progressive disease of the cranial nerves. After two years' experience the author regards this sign as a useful aid in the diagnosis of peripheral facial paralysis.

HART, Greenwich, Conn.

PATHOLOGIC AND ESPECIALLY CYTO-ARCHITECTONIC LESIONS IN PARKINSONISM DUE TO EPIDEMIC ENCEPHALITIS. A. CATALANO, Riv. di neurol. **3**:424 (Sept.); 477 (Nov.) 1930.

The author reports a detailed and careful histologic investigation of two cases of encephalitic parkinsonism. He concludes that, although in parkinsonism there are several reasons in favor of systematic lesions, in chronic encephalitis there may be a more general toxic action due to the chronic infection. Altogether, he believes that lesions responsible for the Parkinson syndrome may involve an extensive system which includes the frontal cortex, the locus niger, the pallidum, the putamen and other pathways of connection. The regions that are more severely involved are the frontal cortex and the substantia nigra. Palilalia may be the result of lesions in the insula and the temporal lobe. The particular defect of speech resembling stammering is to be correlated with lesions in the putamen and optic thalamus and also with lesions in the pons and medulla oblongata. Lesions in the cortex and subcortical structures throw light on the abnormal mental reactions observed in cases of parkinsonism. The cytoarchitecture may be disturbed all over the cortex of the brain, but particularly in the frontal area. Of the cellular layers, those most involved are the layers of large pyramidal cells, small pyramidal cells, and multiform cells. It seems that the pyramidal layers have greater susceptibility to the toxic infection that is at the base of epidemic encephalitis.

FERRARO, New York.

THE CHOROID PLEXUS OF FISHES AND THE QUESTION OF THE ORIGIN OF CEREBROSPINAL FLUID. FERNANDE COUPIN, Schweiz. Arch. f. Neurol. u. Psychiat. **26**:227, 1930.

In this paper the fluid in the subarachnoid space is referred to as cerebrospinal fluid and that in the ventricles of the brain as ventricular fluid. In some of the fishes studied, the choroid plexus was well developed, but there was no subarachnoid space and consequently no cerebrospinal fluid in the sense in which the term is used. In other fishes an abundant supply of fluid was found in the subarachnoid space although the choroid plexus was poorly developed, while in others the fluid was scanty and the plexus well developed. Although he examined serial sections, the author was unable to find any opening that might serve as a means of communication between the ventricular system and the subarachnoid spaces. He concludes from these observations that there is no basis for believing that the cerebrospinal fluid of fishes is formed by the choroid plexus. As the cells were ciliated and as he was able to demonstrate movement of the tufts, the author is inclined to think that the choroid plexus influences the movement of ventricular fluid. The cerebrospinal fluid, he believes, is a dialysate comparable to pericardial, pleural and amniotic fluids.

DANIELS, Rochester, Minn.

VIRILISMUS PROSOPOPILARIS AND ANDROPHANIA IN INSANE WOMEN (INSANE WOMEN WITH BEARDS AND MASCULINE FACE). M. LEVI BIANCHINI, Arch. gen. di neurol. e psichiat. **11**:121, 1930.

The author, in reporting personal observations on eight cases well illustrated by thirteen plates, reviews the subject of masculine secondary sex characters in

women, with special reference to the abnormal growth of hair on the face. The phenomenon of facial hypertrichosis is observed in various endocrinal and mental diseases; this phenomenon, however, is not necessarily of pathologic significance because it may exist in otherwise normal persons, being merely a racial or hereditary feature. As to the ontogenesis of hirsutism in all cases, whether normal or pathologic, the most plausible hypothesis is the one accepted now with regard to hermaphroditism, namely, the coexistence in the embryo of the chromosomes of two sexes in a dominant or in a recessive evolutional and functional state. The sexual orientation of the individual is conditioned by various factors, physiologic, developmental (growth and involution), exogenous (diseases), racial and hereditary. Hirsutism may be explained either as the persistence or as the reactivation of the heterosexual (recessive) state of the individual, caused by morbid factors inhibiting the dominant monosexual state and giving rise to the development of the heterosexual secondary features.

YAKOVLEV, Palmer, Mass.

LYMPHOSARCOMA WITH INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM. C. DAVISON and J. J. MICHAELS, Arch. Int. Med. **45**:908 (June) 1930.

To the single case reported in the literature of lymphosarcoma involving the central nervous system, Davison and Michaels add seven, four having been confirmed by autopsy. In one of these, the case of a man, aged 45, with cranial nerve symptoms and severe lumbar pain, there proved to be a lymphosarcoma, involving the skull and causing pressure on the brain. One patient was a man, aged 32, with the symptoms of myelitis, ataxia and nystagmus, who was found to have a tumor of the lung extending into the spine which caused a degeneration of the posterior columns. Another was a man, aged 40, whose symptoms were largely pleural. He had an extradural mass at the level of the sixth thoracic vertebra. There was one woman in the series, aged 61, whose complaint was abdominal pain, and who gave the appearances characteristic of myelitis. She had a mass dorsal to the cord at the level of the twelfth thoracic vertebra. In no case was there direct involvement of the brain or the tissue of the cord, the neurologic symptoms being due to compression. The authors advocate radium therapy and deep roentgen treatment as the best palliative measures.

DAVIDSON, Newark, N. J.

THE DEVELOPMENT OF THE EAR OF ACANTHIAS VULGARIS. D. P. QUIRING, J. Morphol. & Physiol. **50**:259 (Sept. 5) 1930.

The first indications of auditory vesicles in *Acanthias vulgaris* occur in embryos of from 3.5 to 4 mm. in length, consisting of thickened ectodermal areas composed of large columnar cells. No indication of the invagination of the placodes is present in this stage. In embryos of from 8 to 12 mm. in length, increase in size without differentiation has taken place. In embryos from 15 to 20 mm., differentiation has set in; this is most apparent in the bulging of the walls of the vesicles, indicating the position of future canals. The endolymphatic duct is present. The vesicle is attached to the ganglion of the auditory nerve. A well differentiated sacculus and utriculus, as well as the lagena, are first noted in the 22 mm. stage. Complete separation of the canals, the utriculus, the sacculus, the lagena and the recessus utriculus has taken place in the 30 to 38 mm. stage, together with definite innervation of the ampullae and other sensory areas. The three ampullae are lined with ciliated sensory cells as well as the recessus utriculus, macula neglecta, sacculus and lagena. The utriculus has no sensory patch. The adult structure has three canals, three ampullae, a sacculus, utriculus, lagena, recessus utriculus and rami of the eighth nerve supplying the separate parts. The endolymphatic duct remains open to the surface in the adult form.

WYMAN, Boston.

THE OCULAR MANIFESTATIONS OF SYMPATHETIC NERVOUS SYSTEM HYPERACTIVITY IN CONDITIONS OTHER THAN EXOPHTHALMIC GOITER AND ESPECIALLY IN ESSENTIAL HYPERTENSION; "LIDSPASM," A NEW EYE SIGN. HARRY B. FRIEDGOOD, Am. J. M. Sc. **180**:836 (Dec.) 1930.

The historical significance of exophthalmos is discussed from the anatomic to the clinical aspect. After the common ocular signs associated with hyperactivity of the sympathetic nervous system are detailed, the author presents a new ocular sign, termed "lid spasm." It is determined in the reverse manner to that for the von Graefe sign, in that the object is moved in an upward direction. The upper eyelid is now retracted in advance of the moving eyeball, and a rim of white conjunctiva appears above the cornea if the "lid spasm" sign is positive.

In 258 patients with hypertension, 44 per cent had definite ocular signs, whereas in 236 patients without hypertension, 21 per cent had ocular signs. The relative frequency of these signs seemed to be directly proportional to the degree of systolic hypertension. From the observations the author makes some generalizations, such as the possibility of a fundamental sympathetic disturbance common to hypertension and sympathicotonia, and the state of flux in the tonicity of the sympathetic nervous system.

MICHAELS, Detroit.

EVIDENCE SHOWN IN ROENTGENOGRAMS OF CHANGES IN THE VASCULAR TREE FOLLOWING EXPERIMENTAL SYMPATHETIC GANGLIONECTOMY. BAYARD T. HORTON and WINCHELL MCK. CRAIG, Arch. Surg. **21**:698 (Oct.) 1930.

To find the explanation for the beneficial results following ganglionectomy in Raynaud's disease and in other vascular lesions, Horton and Craig performed the operation on dogs and studied the subsequent anatomy of the blood vessels. In each animal the lumbar sympathetic ganglia and connecting rami were removed from one side; after an interval the dog was bled and metallic mercury was injected into the arteries. In a second series of experiments, periarterial sympathetic neurectomy was done, and the vessels were subsequently injected with the drug. Roentgenograms were taken and the caliber of the blood vessels noted. Definite dilatation of the arteries was seen in comparing the operated and the untreated sides in the ganglionectomy group; the larger vessels in each case were on the operated side. These changes were not observed following sympathetic neurectomy. These experiments lead Horton and Craig to believe that the clinically noted vasodilatation following ganglionectomy is an anatomic fact.

DAVIDSON, Newark, N. J.

HISTOLOGIC OBSERVATIONS ON THE SYMPATHETIC FIBERS. GENEROSO COLUCCI. Riv. di neurol. **3**:386 (Sept.) 1930.

The author studied optically the fibers of the sympathetic system in order to establish the anisotropia and proteotropia resulting from the presence, if any, of myelin sheaths in the sympathetic fibers. The author has also paid special attention to the existence of the so-called crosses of Ranvier which are commonly observed in the fibers of the cerebrospinal system. Colucci concludes that not only is the so-called Latin cross of Ranvier present in the sympathetic nervous system, but that the fibers possess a small amount of myelin as evidenced by the double refraction under the polarized light. The double refraction of the sympathetic fibers had been previously established by Diamare in rami of the splanchnic nerve. Colucci investigated the existence of the myelin sheath in the solar plexus. He concludes that the conception of the sympathetic fibers as nonmyelinated fibers must be changed and asserts that these fibers do possess a small amount of myelin. The possession also of the characteristic of the cross of Ranvier serves to establish an identical fundamental constitution between the sympathetic fibers and the cerebrospinal nerves.

FERRARO, New York.

PITUITARY HEADACHE. LAURENCE H. MAYERS, Endocrinology **14**:319 (Sept.-Oct.) 1930.

The author discusses in detail 5 cases in which the clinical picture and the course under treatment were said to be typical of a series of 60 cases considered under the general heading of pituitary headache. The 60 cases represented a series of patients selected from a service of 900 patients per year for four years. The usual subjects of pituitary headache are said to be obese women of short waisted build, who are energetic, alert and intelligent. All are subject to disturbances of menstruation. All present the common history of onset at adolescence, during the first years of married life or subsequent to childbirth. There is often more than one case in a family. The patients presented were all treated by hypodermic injections of solution of pituitary and all became practically well and remained so for considerable periods of time.

Mayers states that pituitary headache occurs only in women, and that headache in men does not respond to pituitary therapy. In the pituitary headaches of women, pituitary extract by injection is the only effectual remedy. Administration by the mouth is not satisfactory. Pluriglandular therapy is valueless. The author also states that the use of thyroid extract is contraindicated. Menstrual disturbances associated with pituitary headache are usually relieved by the pituitary therapy.

WAGGONER, Ann Arbor.

AN OPERATION FOR THE TREATMENT OF SPASMODIC TORTICOLLIS. W. E. DANDY, Arch. Surg. **20**:1021 (June) 1930.

Since torticollis is never restricted to the muscles of one side, no unilateral surgical procedure can possibly be of value. A bilateral section of the nerves is necessary. Dandy believes that the intradural approach is safer and simpler than cutting the nerves at the intervertebral foramina, as Finney does. He exposes the spinal cord by a high cervical laminectomy and cuts the motor roots of the first three cervical nerves. In an addendum to this paper, he mentions the modification in the procedure by which the sensory roots are avoided. When the central operation is concluded, Dandy turns the patient on his back, makes two incisions in the neck and cuts the accessory nerve peripherally. As a result of this operation, the patient may complain that his head feels a little insecure, but he soon trains himself to use the preserved muscles. In Dandy's series there was no operative mortality, although one patient died of pneumonia almost a month after the operation. Of the seven patients who lived, two were much improved and five were cured. Considering its superiority both in safety and in certainty of result, Dandy believes that intradural section of the eleventh cranial and the first three cervical nerves is the best surgical procedure in the management of torticollis.

DAVIDSON, Newark, N. J.

THE PROBLEM OF PYKNOLEPSY AND ALLIED CONDITIONS. J. RATNER, Arch. f. Psychiat. **89**:802, 1930.

The author discusses the concept of pyknolepsy, which was first described by Friedmann, and its relation to allied states such as epilepsy and narcolepsy. He reports on case in a girl, aged 16, in whom attacks of pyknolepsy developed following an acute attack of epidemic encephalitis. He starts out with an attempt to differentiate the attacks of pyknolepsy from the absences that occur in the course of epilepsy. In the latter there is usually a gradual change of character and deterioration. In diagnosis one also has to consider the peculiar forms of absences that occur with atypical convulsive phenomena in such conditions as tumor of the brain, chronic alcoholism, lead poisoning and hysteria.

As a pathognomonic triad of pyknolepsy the author considers the absence of changes in character or dementia, the large number of attacks (up to 100 daily)

and the onset early in childhood. The occurrence of isolated convulsions should not necessarily speak against the diagnosis of pyknolepsy as long as the triad mentioned is present. They prove that in general the pyknolepsies belong to the wider field of the so-called epilepsies.

MALAMUD, Iowa City.

EXPERIMENTAL LESIONS OF THE BRAIN FROM CARBON MONOXIDE. C. B. SEMERAK and L. H. BACON, Arch. Path. **10**:823 (Dec.) 1930.

Experiments have demonstrated that the effect of carbon monoxide varies in different animals; that the gas is rapidly eliminated by rabbits and guinea-pigs; that rabbits are especially resistant to it, and that the weight of the animals, the amount of the gas and the manner of administration modify its action. Symmetrical lesions in the brains of dogs and more rarely in those of guinea-pigs and rabbits, lesions resembling those occasionally found in human brains, may be produced experimentally by injecting the gas into the arterial blood stream or by having the animals inhale pure carbon monoxide or illuminating gas. When pure carbon monoxide is injected into the blood stream, it combines so rapidly with the hemoglobin that the gas does not cause embolism, or at least not with doses such as were injected in these experiments. Ten cubic centimeters of air alone injected into the carotid arteries of dogs causes severe convulsions, is more frequently and speedily fatal than a similar amount of carbon monoxide, and results in fewer gross changes, these being rarely in the basal ganglia.

WINKELMAN, Philadelphia.

CAR SICKNESS. J. E. LEBENSOHN, Arch. Ophth. **4**:342 (Sept.) 1930.

The relationship of an ocular nystagmus and car sickness is discussed. The nystagmus is induced by the moving landscape with its quick component in the direction of the moving train. Ocular imbalance and ametropia apparently predispose to this condition. Nausea, pallor and dejection, sweating, salivation and pilomotor changes, due to a reflex spread from the sympathetic nervous system, indicate to a certain extent the profound effect of gastric depression or inhibition preceded by duodenal antiperistalsis. These last are considered to be the cause of this pathologic state. The author states that nystagmus, per se, plays little if any part, but that labyrinthine irritation causes various depressive gastric phenomena and the inhibition of gastric hunger contractions. This work has been checked by laboratory studies and kymographic tracings of the movements of the empty stomach throughout the development of an ocular nystagmus by means of labyrinthine irritation with cold water douching and through roentgenograms of the stomach after barium meals.

SPAETH, Philadelphia.

VISUAL PERCEPTION. A. QUIDOR and M. HERUBEL, Ann. d'ocul. **167**:185 (March) 1930.

Researches by Quidor and Herubel confirm the conclusion of a thesis presented to the Faculty of Sciences at Paris in 1909 entitled "Stereoscopic Study and Contribution to the Physiology of Visual Phenomena." In the previous communication they showed that the sensation of relief given by the stereoscope is due, not to the geometric reconstruction of the objects viewed, but to the psychic fusion of their images. They present a new experiment which demonstrates that convergence and divergence may be completely suppressed without impairing the sense of relief. The sensation of relief obtained by monocular observation of two images is in its effect identical with that given by their observation with the aid of a stereoscope. They conclude that the perception of relief is truly monocular; that it is found in all animals, whether the eyes are placed laterally or forward as in man. Binocular vision is not indispensable to the perception of relief, as this is also produced, possibly to a lesser degree, by monocular observation.

BERENS, New York.

CELLULAR STRUCTURE AND CYTO-ARCHITECTURE OF THE CLAUSTRUM. G. PINTUS SANNA, Riv. di neurol. **3**:289 (July) 1930.

The author reviews the conceptions that the claustrum is a dependency of the cerebral cortex or of the corpus striatum (Sterzi, DeVries, Brodmann, Meynert, and others), and that the claustrum is an independent organ (Cajal, Mondino and von Economo). He has studied the cellular structure of the claustrum in adults and in human embryos of between 5 and 9 months, paying attention to the size, shape, cytoplasm, chromatin substance, neurofibrillar reticulum, nucleus, processes and the iron and fat content of the cells.

The author concludes that there is no resemblance between the cells of the putamen and the cells of the claustrum. There is a point of resemblance between the shape of the cells of the claustrum and those of the sixth layer of the cortex (insula), but other factors establish a very definite difference between the two regions. These factors are the volume of the cells, the number of cells, the distribution of the cells, and the direction of the axons.

The claustrum is, therefore, an organ entirely distinct from the putamen and from the cerebral cortex (insula).

FERRARO, New York.

TOPOGRAPHIC RELATIONSHIP BETWEEN THE NERVE PLEXUSES AND LYMPH NODES OF THE ABDOMEN. F. KISS, Arch. Surg. **21**:405 (Sept.) 1930.

To explain the frequency with which inflammatory processes and metastases in the abdominal lymph nodes caused pain and functional disturbances, Kiss investigated the topographic relationships of the organs involved. He found that the left paracardial lymph glands lay directly on the gastric branches of the left vagus and showed that disease of the former structure might readily influence the pneumogastric nerve. The hepatic nodes and hepatic plexuses are also in intimate anatomic relationship, while the pancreatic lymph glands and the nerves to the head of the pancreas are similarly related. Topographic juxtaposition was also noted between the nodes at the duodenojejunal flexure and the superior mesenteric plexus. These relationships, Kiss believes, account for many of the postoperative neurologic complications associated with abdominal operations, and would also explain the irritative and paretic nervous symptoms associated with hyperemia, enlargement and other pathologic changes in the abdominal lymph nodes.

DAVIDSON, Newark, N. J.

THE DISTRIBUTION OF LIPOID IN A CASE OF NIEMANN-PICK'S DISEASE ASSOCIATED WITH AMAUROTIC FAMILY IDIOCY. HARRY SOBOTKA, EMANUEL Z. EPSTEIN and LOUIS LICHTENSTEIN, Arch. Path. **10**:677 (Nov.) 1930.

The peculiar perversion of lipoid metabolism in Niemann-Pick's disease has in recent years aroused considerable interest. The clinical and anatomic features of the disease have been amply elucidated and its differentiation from Gaucher's disease has been established. Whereas in Gaucher's disease, kerasin has been identified as a lipoid specific for this condition, the scattered chemical analyses of spleens in Niemann-Pick's disease suggest merely a general increase of the normal lipoids, especially of phosphatides and cholesterol. The distribution of lipoid in the few livers analyzed has shown a similar tendency.

The analysis of the lipoids of spleen, liver and brain in a case of lipoid histiocytosis (Niemann-Pick) associated with amaurotic family idiocy showed: (1) the disappearance of neutral fat; (2) considerable increase of phosphatides and cholesterol, particularly cholesterol ester, and (3) the absence of kerasin.

WINKELMAN, Philadelphia.

REMARKS ON THE PATHOGENESIS OF GRAVES' DISEASE. DAVID MARINE, Am. J. M. Sc. **180**:767 (Dec.) 1930.

In a clear, concise manner, the author expresses his broad point of view regarding the pathogenesis of exophthalmic goiter. He suggests a simpler classification of the disease into acute and chronic forms, with further subdivisions of complete and incomplete forms. The pathologico-anatomic changes are constant and not specific, and the thyroid gland is a labile tissue with a single morphologic cycle. An important feature is the hyperplasia of the lymphoblastic tissues, the thymus, spleen and regional lymph glands, which the author interprets as a compensatory reaction against some suprarenal-gonadal insufficiency. The frequency of atrophic changes in the liver is looked on as a manifestation of atrophy due to exhaustion. Interesting experimental evidence is cited in support of the view that a deficiency of some internal secretion of the suprarenal cortex and sex glands is one of the fundamental factors in the etiology of exophthalmic goiter.

MICHAELS, Detroit.

THE BOLTZ (A. A. S.) TEST IN CEREBROSPINAL FLUID. BURNHAM S. WALKER and FRANCIS H. SLEEPER, Am. J. Psychiat. **10**:229 (Sept.) 1930.

By mixing 1 cc. of spinal fluid with 0.3 cc. of acetic anhydride and then adding 0.8 cc. of concentrated sulphuric acid, a blue or lilac color will develop within five minutes in the presence of sufficient protein. This is known as the Boltz test and was originally projected as a method of demonstrating the existence of dementia paralytica. Walker and Sleeper, however, show that it is really a test for the tryptophan group of proteins; it is not, they demonstrate, concerned with cholesterol — a widespread error on the subject. Because of the high protein content of the spinal fluid, the Boltz test will be found positive in almost all untreated cases of dementia paralytica. Treatment tends to reduce the intensity of the reaction. With the properly recognized limitations, the Boltz test is a valuable and rapid method of estimating the protein content of spinal fluid.

DAVIDSON, Newark, N. J.

A CASE OF MYOTONIA WITH A STRIKING REACTION TO PILOCARPINE. G. H. MONRAD-KROHN, Acta psychiat. et neurol. **5**:241, 1930.

This is a brief report of a case of myotonia of ten years' duration. The blood calcium was 11.2 mg. per hundred cubic centimeters. The creatinine excretion for twenty-four hours varied between 1.48 and 1.93, i. e., the average excretion was normal, but the daily variations were greater than usual. Immersion of the hands in warm water and intravenous injection of 0.0075 Gm. of pilocarpine caused a dimunition of the manifestations of myotonia. (The author points out that, in view of the hypothesis that myotonia is due to a disturbance of the sarcoplasm, it is of interest that pilocarpine, a drug irritating the parasympathetic nerve had this influence.) Hyperventilation produced the symptoms of tetany plus an excessive restlessness and finally a tonic fixation of all four limbs, the upper slightly abducted at the shoulders and flexed at the elbows, the lower in extreme flexion.

PEARSON, Philadelphia.

LIPOID SUBSTANCES IN THE PITUITARY GLAND OF NORMAL MAMMALS AND MAMMALS WITH CEREBRAL LESIONS. V. DESOGUS, Riv. di pat. nerv. **36**:31 (July-Aug.) 1930.

The author studied the occurrence of lipoid metabolism during sexual activity in dogs and the content in lipoid of the pituitary gland. He also studied dogs in which cerebral lesions had been produced and which were, according to Ceni's investigations, in a condition of sexual hypo-activity. He concludes that in dogs of both sexes in periods of full sexual activity the hypophysis, which presents characteristics of hypo-activity, is free from lipoid content. Conversely, in dogs of

both sexes following a lesion of the brain, and therefore in a condition of sexual hypo-activity, the hypophysis which is hyperactive discloses a very rich content of lipoid substance. The author, therefore, emphasizes the physiologic importance of the lipoid substance in the hypophysis as an endocrine product and as an expression of the functional activity of the internal glands.

FERRARO, New York.

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER. W. O. THOMPSON, A. G. BRAILEY, P. K. THOMPSON and E. G. THORP, Arch. Int. Med. **45**:261 (Feb.) 1930.

Most persons can maintain a healthy state with respect to thyroid function on a daily intake of less than 0.167 mg. of iodine. Larger doses, of course, are required in exophthalmic goiter, but little agreement exists as to how much iodine is required in these conditions. With a view to clarifying this subject, the authors studied the effect of varying dosage of compound solution of iodine on the metabolic rate, pulse, weight and other clinical features of seventeen patients suffering from hyperthyroidism. Their conclusion is that 6 mg. of iodine daily will produce a maximum reduction in the metabolic rate of the average patient with exophthalmic goiter. The larger doses generally given are, the authors believe, useless but not dangerous. By using a drop of compound solution of iodine, which contains 6 mg. of iodine, they found that a lowering of the metabolic rate began within a few days of administration and reached a maximum within a week. This, they conclude, represents the optimum dosage.

DAVIDSON, Newark, N. J.

BROWN PIGMENT ON THE FOREHEAD. O. ANDERSEN and T. B. WERNE, Ugesk. f. læger **92**:817 (Aug. 28) 1930.

The condition discussed in this paper appears to be due to the deposit of pigment in the skin of the forehead in certain zones which connect with one another over the face. The color is yellow or reddish brown. The condition seems to be less a result of pathologic hormones and internal secretion than of a disturbance in the vegetative nervous system similar to the corneal ring or alopecia areata. The symptom is especially common in encephalitis and in cases with basal and striatal lesions of the brain. It is apparently founded on a dysfunction of the growth-regulating functions of the midbrain leading to atrophy and pigmentary degeneration. These brown rings are often found in tumors of the hypophysis and in tumors of the cerebellopontile angle. Two cases with this symptom are presented. The authors believe that the symtom is of localizing value in organic diseases of the brain, even if a functional disturbance must be ascribed as the cause of the pigment anomaly. In bilateral organic lesions the brown pigmentation of the forehead signifies a lesion in the base of the brain.

HART, Greenwich, Conn.

THE INTERNAL RETICULAR APPARATUS OF GOLGI. ALDO DEFRISE, Arch. gen. di neurol. e psichiat. **11**:166, 1930.

This article is a critical review and summary of recent researches on the physicochemical nature, morphology and functional significance of the Golgi apparatus. The internal reticular apparatus of Golgi must be regarded as one of the essential cellular components taking an active part in the cell metabolism. The most recent researches lead to the view that in the cytoplasm there exists a particular substance — Golgi substance — which in vivo is not distinguishable. The methods of vital staining with acid colorants cause the precipitation of this substance; vital staining with the basic colorants stains the preformed granules which are probably associated with the functional activity of this substance. The

silver, gold and osmium methods, effecting the precipitation of colloids of Golgi substance, cause the formation of the reticulum of a more or less characteristic aspect. References are given.

YAKOVLEV, Palmer, Mass.

TOXIC DEGENERATIVE MYELORADICULITIS FROM A LARGE RING CELL CARCINOMA OF THE OVARY. V. TRONCONI, Riv. di pat. nerv. **36**:304 (Sept.-Oct.) 1930.

The author describes a case of myeloradiculitis as a complication of malignancy of the ovary. The lesions involving the central nervous system seemed to be independent of direct metastasis to the spinal cord. The author describes histologically the lesions involving the tissue of the spinal cord as well as the spinal roots and emphasizes the predominance of the medullary over the radicular lesions. He discusses the various possibilities as to the pathogenesis of the lesions and excludes the direct action of metastasis as well as their vascular origin while he accepts the toxic degenerative nature of the lesions. As to the mechanism of action of the toxemia, the author offers no explanation.

FERRARO, New York.

MODERN PROBLEMS IN PSYCHIATRY. E. KAHN, Ment. Hyg. **14**:791 (Oct.) 1930.

In the stage of medical history when physicians were proud of being natural scientists, psychiatrists were afraid of being thought metaphysicists if they looked for psychic mechanisms. Then followed what Kahn calls the "either-or" stage of psychiatry, when there seemed to exist an obligation of being a devotee of either the functional or the organic school. Now we have reached a period in which totality of personality plays the important rôle, and psychiatrists will use what seems valid in all hypotheses. Kahn believes that one of the modern problems in psychiatry is the establishment of the borderline between neurology and psychiatry, and that it is wrong to squeeze these two independent sciences into an unnatural marriage. He concludes by looking to mental hygiene as one of the most promising branches of applied psychiatry.

DAVIDSON, Newark, N. J.

OPTIC ATROPHY IN PAGET'S DISEASE. RUDOLF AEBLI, Arch. Ophth. **4**:691 (Nov.) 1930.

This brief article, illustrated with roentgenograms, deals largely with the history of a case of Paget's disease presenting three points of importance: (1) the relative infrequency of optic atrophy in Paget's disease, (2) the unusual ocular symptoms presented and (3) the bony changes that involved primarily the sphenoidal region and caused a partial obliteration of the optic foramina and to a lesser extent the sphenoidal fissures. These are rare observations in osteitis deformans, which constitutes the important and characteristic feature of Paget's disease. Because of the rather infrequent mention of certain ocular symptoms in this disease, clinicians may be at fault at times in their various observations.

SPAETH, Philadelphia.

PERSONALITY CHANGES IN CHRONIC CASES OF ADDICTION TO COCAINE. G. SANTANGELO, Arch. gen. di neurol. e psichiat. **11**:296, 1930.

On the ground of the observation of chronic addiction to cocaine and of an inquiry into the habits of cocaine addicts, the author points to the fact that in some patients personality changes, especially in the ethical and sexual spheres, persist even as long as two years after the subsidence of symptoms of acute intoxication. Not until these personality changes disappear may a cocaine addict be considered as cured. Until then the author recommends detention of such patients in an institution as a prophylactic measure against a relapse.

YAKOVLEV, Palmer, Mass.

EMOTIONAL HYPERTENSION. EDWARD J. STIEGLITZ, Am. J. M. Sc. **179**:775 (June) 1930.

Beginning with the thesis that emotional stimuli cause variations in the arterial tension, eight cases of extreme vascular instability associated with emotional hypertension were analyzed. Among the subjective complaints, sexual abnormalities were most prevalent, making it appear that perhaps some physiologic connection exists between gonadal activity and the stability of vasomotor control. The normal equilibratory mechanism of the circulation is disturbed and an exaggerated, uncompensated response of generalized vasoconstriction occurs on psychic stimulation. The best therapy lies in bismuth subnitrate, in doses of 10 grains three times a day, combined with psychotherapy.

MICHAELS, Detroit.

LABORATORY STUDIES IN EPILEPSY. JOSEPH FELSEN, Arch. Int. Med. **46**:180 (Aug.) 1930.

In the hope of finding constant physiologic abnormalities in epileptic persons, Felsen studied by laboratory methods the various body systems of seventy-three patients suffering from grand or petit mal. He found an increase in the chloride content of the blood in 72 per cent of his subjects. Half of the patients had dental infection; almost 50 per cent were definitely sympatheticotonic, while less than 35 per cent could be classed as vagotonic. Forty-five per cent showed a diminished phenolsulphonphthalein output, while one third had constant glycosuria. Felsen draws no definite conclusions from this statistical survey, but suggests that it reveals enough variation to justify further detailed study of the individual epileptic patient. In the light of the recent emphasis on water metabolism, the large percentage of subjects with high chloride concentration is worthy of note.

TUMORS OF THE ORBIT. I. COHN, Arch. Surg. **20**:906 (June) 1930.

The types of orbital tumors considered by Cohn include the osteomas, melanomas, epitheliomas of the lids and tumors of the lacrimal gland. An osteoma is a rare tumor, characterized by exophthalmos, headache and specific roentgen observations. Because of the effect the pressure of such tumors can produce they must be removed. Melanomas are more common growths and are always metastatic. The only primary carcinoma of the orbit is the cancer of the lacrimal gland. Such tumors are malignant and must be removed radically. Epitheliomas of the lid may be desiccated, but if they recur, and they usually do, exenteration of the orbit is necessary. Each type of orbital growth presented is illustrated by several cases, and microscopic views of the tumors are included.

DAVIDSON, Newark, N. J.

THE USE OF BRACES IN OBSTETRICAL BRACHIAL PARALYSIS. S. W. BOORSTEIN, Am. J. Dis. Child. **39**:1279 (June) 1930.

In most cases of obstetrical brachial palsy, the nerves are stretched, not torn, and the deformity is more serious than the paralysis. For this reason Boorstein recommends that a brace be applied as early as possible. It should be fixed so that the shoulder is abducted, the forearm supinated, the elbow flexed and the wrist extended. To offset atrophy, massage is indicated, and to discourage adhesions and prevent stiffness, exercise is required after the brace is removed. Recovery occurred in almost all of 200 cases in which the patients were treated in this way. The average length of time required for wearing the brace was from three to eight months.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Nov. 20, 1930

A. B. YUDELSON, M.D., *Vice-President, Presiding*

THE EFFECT ON DOGS OF INTRATHECAL INJECTIONS OF MERCUROCHROME-220 SOLUBLE AND METAPHEN. DR. ABRAHAM LEVINSON and DR. MEYER A. PERLSTEIN (by invitation).

From time to time, reports appear in the literature regarding the use of chemical antiseptics in the treatment for meningitis. Our problem consisted of two main questions: 1. Is it safe to use chemical antiseptics intrathecally, and if so in what doses? 2. What is the meningeal reaction following the introduction of chemicals intrathecally?

In intrathecal work it is important to realize the difficulties encountered in performing lumbar punctures on dogs. It is much harder to obtain clear fluid from dogs than it is from human beings, because the cord extends to the sixth or seventh lumbar vertebra instead of ending at the fifth as in a human being. Because of this injuries to the cord frequently follow lumbar punctures in dogs. The cistern in dogs is relatively smaller than in the adult human being. In order to judge the meningeal reaction from the standpoint of cerebrospinal fluid changes, we have studied the cerebrospinal fluid values in normal dogs. We have found that the amount obtainable from the cistern varies between 1 and 8 cc., with a mean value of 3.4 cc. The amount obtainable from the lumbar region varied between 0.5 and 5 cc., with a mean value of 2.2 cc. The pressure, measured in centimeters of water by means of the Claude manometer, varied in cistern punctures from 3 to 23 cm., with a mean value of 14.2 cm. In lumbar punctures the pressure varied from 5 to 18 cm., with a mean value of 12.1 cm. The cells in cistern fluid varied from 0 to 10, with a mean value of 2.9, and in lumbar fluid from 1 to 10, with a mean value of 4.4.

We found that the dose of chemicals depends on the weight of the dog; the larger the dog, the greater the amount of chemical that can be injected. The safe dose of mercurochrome-220 soluble when injected intraspinally is 0.075 mg. per pound of body weight, which equals 0.07 cc. of a 1:1,000 solution, or 0.1 per cent per pound of body weight. The safe dose of mercurochrome when injected into the cistern was found by us to be 0.05 mg., or 0.05 cc. of a 1:1,000 solution, or 0.1 per cent, per pound of body weight. The safe dose of metaphen when injected intraspinally was found to be 0.06 mg., or 0.06 cc. of a 1:1,000 solution per pound of body weight. When injected into the cistern the safe dose was found to be 0.05 mg. or 0.05 cc. of a 1:1,000 solution per pound of body weight.

We found that both mercurochrome and metaphen produced a meningeal reaction manifesting itself in an edema of the meninges, a serofibrinous exudate, perivascular infiltrations of endothelial cells, polymorphonuclear cells and lymphocytes, and often an aseptic purulent polymorphonuclear exudate. Following the intrathecal injection of either metaphen or mercurochrome, changes occur in the cerebrospinal fluid removed at subsequent punctures. The changes may become evident within the first hour and usually disappear before the end of a week. They consist of an increased protein content, to the extent that a coagulum may form, and the presence of numerous red blood cells first, then of polymorphonuclear leukocytes and endothelial cells, and finally of lymphocytes. The fluid may be pink or xanthochromic, and frequently it is turbid. We have also introduced mercurochrome and metaphen into the spine by means of lavage from the cistern

to the lumbar route. We found that mercurochrome cannot be injected into the subarachnoid space in bactericidal doses, while metaphen can be introduced intrathecally in bactericidal doses without ill effect. On the basis of this work we conclude that mercurochrome should not be used intrathecally, as the safe dose is not bactericidal. As to metaphen, we are not ready to recommend it, but we are able to state that it is possible to introduce it in safe doses in bactericidal strength.

DISCUSSION

DR. CLARENCE A. NEYMANN: Were the solutions that were used isotonic?

DR. MEYER A. PERLSTEIN: The solutions were made up in physiologic solution of sodium chloride in the beginning; but since the latter is, per se, an intrathecal irritant, and since we wished to have the solutions as isotonic as possible, the dilutions were later made in spinal fluid by a process of sufflage during the injection. We learned that it is easy to increase the intracranial pressure enormously by the injection of a small amount of solution. We, therefore, controlled the pressure of injection by always having a manometer attached to a needle in the subarachnoid space and by injecting the fluid slowly.

When we lavaged the dogs, we would collect the specimens at the needle of exit at successive intervals and examine them colorimetrically to estimate the strength of the solution in the subarachnoid space at these intervals. We found that as the lavage progressed the concentration of the drug in the collected fluid increased. For instance, ten minutes after the start of the lavage, the concentration of mercurochrome in the collected specimen was 26 per cent of the original solution; five minutes later it was 36 per cent; five minutes later, 59 per cent, and five minutes after that, just before the dog died, it was 62 per cent of the original solution. It seems that the injection of these drugs is followed by an increased secretion of cerebrospinal fluid in an attempt by nature to dilute the irritant injected. Fatigue of the secretory mechanism results in the attainment of a lethal concentration of the drug in the subarachnoid space.

We observed that dogs who died following the injection of mercurochrome, died within thirty minutes of a respiratory death, indicating a direct action of mercurochrome on the vital medullary centers. On the other hand, animals receiving lethal doses of metaphen died from one to thirteen days later, apparently from the resulting aseptic meningitis.

Examinations of the cerebrospinal fluid twenty-four hours after the injection often disclosed a fluid that would drip out slowly, was gelatinous and would clot on standing. Usually, the cell counts were high; but in six dogs, the cell counts were very low, out of all proportion to the amount of albumin that was present. We have not been able thus far to explain the occurrence of this phenomenon of albuminocytologic dissociation in these dogs.

I wish to add that all of the work was done under morphine-ether anesthesia.

DR. A. B. YUDELSON: What was the maximum temperature of the fluid that was injected?

DR. ABRAHAM LEVINSON: The injections were made at 39 C., which is slightly above the normal body temperature of the dog. As the fluid to be injected passed through the apparatus, it cooled slightly, so that it was at the dog's body temperature when it entered the subdural cavity.

We are studying the effect on dogs of intrathecal injection of other chemicals in addition to the ones discussed tonight. I do not know how far we will get with the work, but we have already learned that a meningeal reaction results from the intrathecal injection of any foreign body. This fact should be kept in mind in all experimental work on animals.

THE USE OF SULPHUR FOR THE PRODUCTION OF FEVER. DR. R. P. MACKAY.

This article will be published in full in a later issue of the ARCHIVES.

PSYCHOANALYTIC ASPECTS OF SUICIDE. DR. KARL A. MENNINGER.

While, statistically, death by suicide is relatively infrequent, there is reason to believe, both from the numerous unsuccessful attempts at suicide and from psychoanalytic studies, that incomplete suicide is common and that suicidal tendencies are present in some degree in very many if not all people. In an analysis of the leading forces of suicide one must first dispose of the popular explanation that it is merely an escape from an intolerable situation, a situation which if external and obvious renders the suicide "brave" and if internal and invisible renders it "crazy." The fallacy in this conception is its incompleteness, dependent as it is on the assumption that the force impelling the regression comes wholly from without. From the analytic standpoint it is more important to study the push from within than merely the pull from without, since it is well known that the suicidal person, like many others, often helps to create the very things from which he is taking flight.

An analysis of suicide is made complex by reason of the fact that it combines in one act and one actor several accomplishments. One must recognize it as a peculiar kind of death in which there are three elements: the element of dying, the element of killing and the element of being killed, for each of which there appears to be always unconscious and sometime conscious motivation.

The wish to die is not always present in those who attempt suicide, as is apparent from the almost ludicrous failure of many apparently bone fide attempts. However, it is present, usually deeply buried, in many nonsuicidal persons. There is increasing evidence in the direction of Freud's "death instinct."

The wish to kill is a more familiar motive and represents the extreme of destructive aggression as contrasted with the sexual embrace as the supreme act of creative aggression. It is dictated by a primary motive of defense stimulated by fear, a secondary motive of revenge stimulated by hate aroused by the fulfilment of fear and a tertiary motive of erotism stimulated by the sadistic gratifications afforded in the attack. All this destructive aggression can be visited on the self by the simple mechanisms, well known in analysis, of introjection and displacement. The hated or feared or loved object is introjected into the self, and the unconscious emotional attitudes are then visited on this individual as incorporated within the ego. Illustrations of this are submitted, taken from every day life and from some specific instances of suicide. In such a common instance, for example, as the suicide of the jilted lover, one sees the attack on that part of the lover which is still available to attack, namely, the introjected portion.

The wish to be killed, the third component of suicide, is the extreme form of submission, and comprises masochistic satisfaction with the need for punishment arising from a sense of guilt, usually referable to the hostile and aggressive desires just discussed. Having indulged in forbidden wishes or acts of aggression, the ego is oppressed by an anxiety of guilt which can be assuaged only by punishment in kind. This is apparent in the details of many suicides.

The exhibitionistic satisfactions of suicide are probably related to this masochistic satisfaction in submitting oneself to the attack of others. Special cases of suicide, such as suicide pacts and the combination of suicide with murder, can also be shown to confirm this analysis.

Of great practical importance is a recognition that these motives in the direction of self-destruction, while dramatically represented in extremes by frank suicide, are clearly recognizable in less complete forms in many persons. Instead of a consciously deliberated, quickly executed, completely and directly achieved act, suicide is more often a slow, gradual, oscillating, indirect achievement, and instead of conscious and external motives being predominant, internal and unconscious motives are likely to be far more important. In fact, a considerable body of psychotherapeutic endeavor lies in the direction of deflecting to better objectives unconscious, self-destructive tendencies, which in the overt form are called suicide.

DISCUSSION

DR. RALPH C. HAMILL: Working with children, I think that I can bear out Dr. Menninger's assumption that a death wish is tremendously frequent, if not universal, in children. I have come to think that every child who dreams of ghosts is murdering his parents, for every child with whom I have been able to work out this dream has shown that the parent appeared in the background very soon. After all, a ghost is the spirit of the dead. Along the lines of Dr. Menninger's division into three parts, the ghost is a fearsome thing to the child. In other words, the child has a distinct feeling of guilt about it.

I saw a patient recently in whom, after coming down stairs from choosing an apartment for her mother following her father's death, the left side of the body suddenly became numb. Because of some dreams associated with masturbation, the father was associated with the left side of her body. This was identification, one may say, and at the same time one of the partial suicides of which Dr. Menninger spoke.

DR. A. A. LOW: It is important that psychologic views should be submitted to experimental verification. In psychoanalysis one goes back to the earliest experiences of the child and deals with the memories of the adult which are not always trustworthy. It should be possible to experiment even on such entities as the Oedipus constellation. At least, an attempt should be made.

In the course of an extensive investigation of speech disturbances, it was necessary to study the development of speech in normal children. At present, three children are being studied, ranging from 2½ to 3½ years of age. The parents, all college graduates, are instructed to take down as far as possible every utterance of the child. The notes are then arranged and tabulated. Some experimentation is carried on with regard to time and space perception, recognition of colors and understanding of numbers. Incidentally, it was noted that the pronounced attachment of the children to the heterosexed parent was subject to some fluctuation. Two of the children spontaneously shifted their attachment from the heterosexed to the homosexed parent. The father whose child had not yet effected the shift was instructed to become strict with his daughter in order to see whether the child would turn away from him toward the mother. While such experiments are not conclusive and not strictly "experimental," I think that they offer the possibility of furnishing more reliable material than can be gathered from the questionable reminiscences of adults.

DR. CLARENCE A. NEYMANN: I am analyzing a woman with a depression. She has a father fixation which has persisted throughout her life. As a result of the hatred of the father, because of unrequited love she has now transferred this hatred to her husband who symbolizes the father fixation. She is very depressed. Another patient committed suicide at the beginning of the analysis.

DR. GEORGE W. HALL: The general practitioner is not educated to a sense of duty regarding patients who attempt suicide. He does not sufficiently recognize the depressed condition in these persons. They may have a manic-depressive psychosis in which the depression may last only a few days, the patient then becoming normal, which in turn is followed by a hyperactive state for a few days.

DR. ALFRED P. SOLOMON: In the spring, 1924, a young woman and, shortly after, her husband came to the examining room of Cook County Hospital saying that they had taken mercuric chloride for the purpose of committing suicide. They were taken care of by the same junior intern who accepted at face value the histories and gave them what he supposed was the Rosenblum treatment. Instead of giving the solution of sodium bicarbonate intravenously, however, in both instances he gave it under the breasts. When a report from the coroner's chemist showed that no mercuric chloride had been found in the contents of the stomach, neither patient would admit that none had been taken. As a gangrenous slough began to form at the site of the injections of sodium bicarbonate, the patients seemed unperturbed and were reported to be exultant at their suffering; each sent a note to the other telling the details of his terrible symptoms. It was not

until it became evident that the condition was serious and each was told that the other might die that they confessed that they had not taken mercuric chloride, but that the whole affair was simply a huge hoax to make the one feel sorry for the other. It is reported that the episode had followed a family argument over a trivial situation. When it became obvious that they were actually going to die, both made a first real struggle for life, losing the self-satisfied composure which had heretofore been present.

Both died from the toxic effect of the gangrenous sloughs.

DR. KARL A. MENNINGER: I have a feeling that the material of dreams somewhat stimulates resentment on the part of persons for whom dream stuff seems negligible material. At one time, however, examination of the urine was objected to as a silly and pointless procedure; ultimately it was found that by examining the urine one could ascertain something about the organs that excreted it. Similarly with dreams, by studying them one may find out something about the organism that creates them. Unfortunately, so many of our colleagues do not yet have this realization, that I do not believe discussions of dreams have as much value as they should.

The point made by Dr. Low about experimentation is one concerning which many psychologists are extremely sensitive. I think that this is because we distrust introspection. The material Dr. Low presented is no more accurate experimentally than he can find in any work in the analysis of children. The manner in which he discussed the matter shows clearly that his understanding of the psychogenic theory is incomplete. We are not interested alone in the conscious manifestations, but rather more in the unconscious libidinous tendencies. We are talking about the human psyche, and since one cannot experiment on human beings and lower animals do not have the same psyche, one must depend on inductive material.

Dr. Neymann asks what to do with "red hot cases" of depression. I can tell you only that such cases are probably not at that time susceptible to beneficial psychoanalysis. It is difficult to accomplish anything with them or with less acute cases in the same environment. This is so evident that at our clinic we are building a new hospital building so that we can have patients who are capable of psychoanalysis in a different setting from those who are more psychotic. My point is that patients in whom psychoanalysis is of value are those in whom the suicidal element is definitely incomplete, and those in whom we wish to interest the general practitioner as to his responsibilities in preventing suicide are not benefited at that time by analysis.

General practitioners, as Dr. Hall said, are not acquainted with these things. This is even more true in the cases of partial suicide such as those with which Dr. Stewart Sniffen is working at the University of Chicago. This includes the students who go to the University for the purpose of getting an education and yet do everything possible to prevent themselves from getting it. Dr. Sniffen has a colossal job, for there are hundreds of students who need help of this kind. It is known that Abraham Lincoln, on at least two occasions, was prevented from suicide. Many persons who seem to have self-destructive tendencies can be prevented from suicide.

I do not think that insurance companies have yet come to grips with this matter. I was once asked by an insurance man how many suicides I could predict. I said I did not know exactly. Could I predict one tenth of the cases? I said that I thought so. Then he said, "If you can, you could save us millions of dollars."

I shall add a final word as to exhibitionism in suicide. Everyone knows that many persons who commit suicide appear to get satisfaction from the thought of the spectacle that they will offer in their death, partly because they enjoy the attention they receive, partly because they dramatize their own existence and magnify their own ego. All of this I think is derived from masochistic tendencies —"I will do anything at all if you will only give me a little attention." Such a person becomes a clown and endeavors to dramatize his suffering for the sake

of getting attention, even at an enormous cost to himself. I think that this is what is called a secondary or epignosic gain, differing from the real motive, just as a neurotic person may use her condition to secure certain advantages. In the instance cited by Dr. Solomon, the question of satisfaction in suffering finally became the great thing, whereas at first the threat of suicide was the great thing. A fake suicide does not look like self-inflicted punishment, but it really is. It is a game for obtaining more suffering.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Nov. 28, 1930

WILLIAMS B. CADWALADER, M.D., *President, in the Chair*

A CASE OF HEMATOMYELIA. DR. GEORGE WILSON and DR. R. M. LEWIS.

J. N., a white man, aged 47, was admitted to the men's alcoholic ward on Oct. 14, 1930, his chief complaint being of weakness in the arms and legs. He had been suffering from the malady for ten days. Saturday night, October 4, he spent at the home of a friend, drinking a few glasses of beer and retiring at about 10:30. He stated, however, that he was not under the influence of alcohol at the time. At about 11 o'clock, he arose and was making his way to the bathroom through an unfamiliar and unlighted hallway, when he stepped onto a staircase and tumbled headlong to the floor below. He remembers that he hit the back of his neck and that he did not lose consciousness. He thinks that he remained at the foot of the stairs for about an hour before he was found. At the time he was apparently dazed, but when assisted to his feet he was able to make his way with assistance; he was pushed up the stairs and went to bed. He slept through the night. In the morning he had pain at the back of the neck and remained in bed the entire day. He did not leave the room, but was able to get out of bed to attend to natural urges. At this time he noticed no disturbance of sphincteric control. He arose on October 6 with the intention of going to work, but after taking a few steps the pain in the neck became so severe that he went back to bed. There was some weakness of the arms and legs at this time, and on October 8, the fourth day after the fall, he was unable to get out of bed. On October 10, the patient summoned a physician, who visited him again on October 11 and 13. On October 14, the patient was taken to the hospital.

The history taken in the alcoholic ward relating to the use of alcohol was as follows: The patient said that he had drunk ½ pint of liquor daily up to October 4, when he felt ill and did not want any more. His arms had begun to get stiff at this time. He fell down the steps, and had not been able to use his hands or feet well since. The history elicited from the patient removes the possible background of alcoholic neuritis. He said that on Saturday nights, he and his friends were in the habit of drinking about ½ pint of whisky, and occasionally over the week-end each would drink a pint. During the week he drank little because he could not afford it. Two or three weeks before he tumbled down the stairs he gave up drinking whisky, because it was beginning to make him sick. He worked steadily on his job in a tannery until October 4. His work was with wet hides, and his hands and feet were constantly wet.

He was admitted to the hospital on the tenth day after the accident.

Physical examination revealed that the pupils were small and reacted sluggishly to light and in accommodation. The ocular movements were full and equal. The blood pressure was 130 systolic and 70 diastolic. The abdominal reflexes were absent. The patient was unable to sit up. He had weakness of both hands. The biceps and triceps reflexes were equal and active. There was a decided loss of power in the lower extremities. The patellar, achilles and plantar reflexes were of the flexor type and equal on the two sides.

The provisional diagnoses at this time were: chronic alcoholism, hysteria (?) and injury to the vertebrae, with compression of the cord.

On the twelfth day after admission, a spinal puncture was performed, and about 15 cc. of yellow fluid was obtained. This was under diminished pressure. A diagnosis suggested at this time was spinal injury with compression of the cord and subarachnoid hemorrhage.

The patient was seen in consultation by Dr. Wilson and transferred to the men's nervous ward. At this time he was well oriented, as he had been during his entire illness. He was able to move the arms and forearms slightly, but not the remainder of the extremities. He was able to move the neck. He had complete loss of the senses of touch, temperature, pain, position and vibration up to the third rib anteriorly and the first dorsal spine posteriorly. There was a similar loss of sensation over the ulnar surface of both arms. The corneal, palatal and pharyngeal reflexes were present. The epigastric, abdominal and cremasteric reflexes were absent. All of the deep reflexes were present and somewhat exaggerated. There was no Babinski or Hoffmann sign and no clonus. The diagnosis at this time was hematomyelia at the first dorsal vertebra with complete paralysis below.

A lumbar puncture at this time showed: pressure, 2 mm. of mercury; jugular compression over one jugular vein caused no rise, pressure over both jugulars caused a very slight rise, if any. The fluid was a deep, cloudy yellow.

On the twenty-fourth day after admission, the patient showed Horner's syndrome on the right side. He was able to move his shoulders and arms and had fair extensor movements of the wrists. He had practically no function of the median nerve, but had some of the ulnar nerve. The abdomen was distended. The lower extremities were immovable, but the reflexes of defense were present. The right patellar reflex was active; the left could not be obtained. Ankle clonus was absent. Plantar stimulation on the right occasionally produced an atypical Babinski sign; on the left no response was obtained.

On the thirtieth day, a combined lumbar and cisternal puncture showed: pressure, 0 and 0; jugular compression on both sides, 10 and 24 and 28; coughing, 2 and 4, and straining, 0 and 0, respectively.

There was a slow drop in the spinal pressure and a quick drop in the cisternal pressure; slightly tinged fluid came from the cisterna, and markedly red-stained fluid from the spine.

On the fortieth day, there was good power in the biceps. The triceps muscle was somewhat weak. Flexion and extension of the fingers could be performed with little force. Fibrillary tremors were not noted. The right pupil was somewhat smaller than the left, but there was no difference in the palpebral fissures. The patient had regained much of the power in the left leg, but less in the right. The sensation of pain was normal over the face, neck and upper part of the thorax to the fourth interspace. On the left the sensation of pain was practically lost below this point except in the foot and leg below the knee. On the right side, the sensation of pain became normal at about the tenth thoracic segment and was normal below, except for an area over the anterior surface of the right thigh. This sensation was lost on the inner side of the arm, forearm and little finger on both sides. Vibratory sense was lost below the costal margin. The sensation of touch was not acute below the line of the nipple. The sense of position in the great toes was definitely impaired. There was more definite recovery of the sensation of pain on the right, and movement on the left showed a partial Brown-Sequard syndrome, so the hemorrhage was most intense on the right, including the sixth, seventh and ninth cervical segments.

On the fifty-second day, a definite return of sensation was noted. Vibratory sense was still impaired in both legs, but it began at the knees and became stronger at the pelvis and still stronger at the costal margin. The sense of position in the great toes was still impaired. Power was returning rapidly, and the movements of the legs were quick and accurate. On this day, the patient was able to feed himself for the first time.

On the forty-second day, a lumbar tap showed: pressure, 10 mm. of mercury; jugular compression, on the right side, to 20 mm., on the left, to 20 mm., and both, to 40; all fell away rapidly.

Fifty-five days after the accident, the abdominal reflexes were absent, the patellar and achilles reflexes were hyperactive, and there was a positive Babinski sign on the right. The patient had improved remarkably both in power and in sensation.

DISCUSSION

DR. N. W. WINKELMAN: I know Dr. Wilson's conservatism well; had the patient been under my care during the first few days, I might have been tempted to consider the case from a different angle. The patient probably had bleeding into the spinal cord, which must have been of such a degree that it produced a great amount of swelling of the substance of the cord, otherwise I see no way in which one can explain the block. I should want to relieve pressure of that sort as quickly as possible. I had the same experience during the World War. Situated as we were behind the lines, many times I was under considerable difficulty in settling the question of whether or not to operate in cases of injury to the cord. We did not know of the Queckenstedt test at that time, although Queckenstedt reported his observations before the war.

Dr. Fay has reported a case of hemorrhage into the substance of the brain with pressure, in which he opened the skull and aspirated the hemorrhage. I do not see any serious objection to doing the same thing in this case, even though operation would involve the spinal cord. With the cord under a pressure of this sort, it does not take long for destruction to take place. What objections would Dr. Wilson have to decompression? At Blockley, there are surgeons who are capable of opening the cord without trauma.

DR. MILTON K. MYERS: This case recalls the almost identical symptoms and history of a patient with chronic alcoholism at the St. Agnes Hospital; he suffered from trauma of the cervical region of the spine, without fracture of the vertebrae. This patient was treated expectantly. Bed sores developed early. There was no blood of consequence in the cerebrospinal fluid; on the other hand, it was markedly yellow. There was an early marked rise in temperature, leading us to believe that we might be dealing with a case of myelitis. There has been no return of movement in the legs, although the arms are much better than when the patient was brought to the hospital. Dr. Wilson is entirely right. Operative intervention is not indicated in this class of case. Many patients do well without it. In the case under my charge the patient's bed sores interfered with recovery.

DR. ALFRED GORDON: I am surprised at the extreme conservatism of Dr. Wilson. If, as he says, operations should not be performed in cases of injury to the spine, what would he say of the traumatic cases in which the cord was found uninjured, but in which a hemorrhage was surrounding it and pressing on it? Would he not regret not having removed the hemorrhage? Such cases have been reported and have been observed. Personally, I have observed cases in which a broken vertebra pressed on the dura of the cord, and in which prompt operation restored the integrity of the surface of the nerve tissue with excellent results. A discrimination should of course be made, but from personal experience I believe that in every traumatic case in which there are symptoms in the spinal cord operation should be performed immediately if the patient's general condition permits. With present methods of neurologic surgery the risk is at a minimum.

DR. RUBIN LEWIS: The initial symptoms came on gradually. In retrospect, one can see how the signs localized at about the fifth or sixth cervical segment. The first signs were suggestive of a lesion at about the first or second thoracic segments. Had a laminectomy been done at the outset, the affected portions of the cord would not have been exposed. The symptoms came on so slowly and the hemorrhage, if it was one, developed so gradually that immediate operation would not have exposed the lesion.

A New Group of Objective Signs of Encephalitis. Dr. Samuel B. Hadden.

No present method of treatment for encephalitis is satisfactory and none will ever be able to influence favorably the well established parkinsonian states; however, their early recognition in incipient form will enable one to apply at an earlier date the known remedies and those that will be advanced in the future. The following symptoms have been noted in all cases of established parkinsonism and were the first signs observed in some cases in which typical signs later developed.

All of the signs are dependent on easy exhaustibility in the performance of rapidly opposed movements: 1. On rapid blinking of the eyelids, the rhythm and amplitude quickly become irregular, and eventually the lids become fixed or there is a rapid fluttering. 2. If the patient is instructed to place the tip of the tongue behind the upper central incisors and to move it rapidly in and out of the mouth, scraping the tip over the teeth in passing, the tongue is straightened out, the movements become slower and irregularities of rate and rhythm develop. The tongue usually shows rapid fatigue and becomes motionless within the mouth. 3. In the incipient parkinsonian state, when the patient is told to smack the lips as rapidly and as loudly as possible, with the teeth firmly approximated, the smack rapidly becomes inaudible and the movement of the lips irregular and ineffective.

After a short study of the normal person in the performance of these tests and comparison with one having an established parkinsonian state, one can quickly learn the abnormal variations in the performance of these movements.

DISCUSSION

Dr. Alfred Gordon: In the test of voluntarily smacking the lips and the rapid voluntary movements of the tongue, were any control cases in normal and pathologic states used?

Dr. A. M. Ornsteen: Any attempt to show early signs of beginning parkinsonism in persons who are known to have encephalitis, is, of course, a step in the right direction. If a specific remedy is ever introduced for this terrible disorder it would be reasonable to expect the greatest improvement in cases that are recognized the earliest. The signs described by Dr. Hadden are based on the ready exhaustibility of muscle power during repeated alternating movements. The triad of signs in the hands that I have described also has this basis. The exhaustibility of the movements of the thumb and forefinger is associated with a gradual lowering of the position of the affected arm during the performance of this test. In Dr. Hadden's blinking test, the orbicularis palpebrarum becomes exhausted; in smacking the lips, the orbicularis oris shows this tendency, and in the test involving movement of the tongue, the lingual muscles are exhausted. Kinnier Wilson has referred to these manifestations as poverty of movement. In the first case shown by Dr. Hadden, in which spontaneous movements of blinking occurred, is this symptom exaggerated on movement of the jaw, since there is a jaw-wink reflex? I have noticed in such cases, namely, those in which there are spontaneous movements of blinking, that when the patient is asked to execute movements, as in chewing gum, the blinking movements are exaggerated.

Dr. S. B. Hadden: I have compared these movements in patients with parkinsonian states with those in large numbers of normal persons and I have found certain facility of movement in the latter that is not present in those having the parkinsonian state.

The patient presented does show some associated blinking with chewing and also has frequent attacks of oculogyric crises. Dr. Ornsteen's mention of the fact that the patient's laughing during the performance of test 3 as a factor complicating the interpretation is important. I think that this can be avoided in examinations made in private.

A Case of Gélineau Syndrome. Dr. A. Silverstein.

In 1880, Gélineau first recognized a condition characterized by two prominent symptoms: (1) attacks of sleep and (2) cataplexy—a sudden relaxation of the muscular apparatus during emotional display. He designated this as a new syndrome which he named narcolepsy. It is not my purpose to comment on the confusion that this term has aroused in the literature. Suffice it to say that it is misleading and does not convey the meaning of the syndrome that Gélineau first introduced. In the literature this condition is described as "true narcolepsy" in contrast to "symptomatic narcolepsy," a designation for those cases in which attacks of morbid somnolence occur as a symptom of some other disease without the presence of cataplexy. This subject was discussed by Dr. Max Levin before this Society last year.

The following case is typical of the syndrome as described by Gélineau.

A man, aged 20, visited the outpatient clinic of Temple University Hospital on Oct. 29, 1930. He had been born at full term and was a normal infant. At 3 or 4 years of age, he had had a severe attack of measles during which he was stuporous for three or four days. On a particularly hot day during the summer of the same year, he had what the mother considered a "heat stroke" or "heat prostration," although the child had not been exposed to the sun. She stated that in this condition he was limp, pale and perfectly relaxed, and appeared semiconscious. This lasted for about two hours, and on the following morning the child was well. Ever since this episode the mother had been exceedingly cautious in protecting him from the heat. He complained of attacks of muscular relaxation, simulating fainting, usually occurring when he was laughing heartily, of drowsiness and somnolence during the day and of occasional headaches. He gave a vague history of diplopia that was momentary and that had occurred for the first time while he was waiting to be interviewed.

According to the patient, he experienced the first attack of cataplexy when he was 14 years of age, in the summer, 1924, while walking with friends at a seashore resort. This he described as a sudden relaxation of all the muscles during a spasm of hearty laughter, following which his body pitched forward so that he fell on his face. He remained this way for about one minute, but did not lose consciousness as he could hear the people talking and walking about him. There was no biting of the tongue, frothing of the mouth or loss of sphincter control. These attacks had recurred since then intermittently, and were usually ushered in by hearty laughter, although they were not always induced by this emotion. Recently they had had a tendency to increase both in severity and in frequency. They were least noticeable a few months before and after marriage, when he was 17 years of age. The patient's wife first recognized this abnormal condition after they had been married three months. He then manifested comparatively mild symptoms in which his head dropped forward on his chest during laughter. For the past two years he would fall either forward or backward, and he usually felt no ill effects following the attack. Although he had never lost consciousness, he claimed to have suffered from injuries to his head and spine several times when falling in an attack. As an illustration, he related the following incident: On Oct. 4, 1930, while cleaning a window in a garage, he saw a dead bird and immediately fell forward on his face, dislodging a dental plate of three teeth; he stated definitely that he was conscious during the entire performance. This was his last severe attack. Whereas in the beginning the cataplectic symptoms were only precipitated by laughter, they could later be induced by anger and sudden emotion. The patient stated that when he got angry, he experienced weakness and felt a relaxation of the muscles of the jaw, head and neck, followed by the drooping of his head, but that he "caught" himself in time to prevent the usual termination in a complete fall. A similar attack was brought about while walking with his wife immediately after she had called his attention to a poster which advertised the unusual exhibit of a whale.

Attacks of sleep were first noticed in the fall, 1925, when the patient began to have periods of sleep at any time during the day. The desire for sleep was

irresistible when the patient was in a restful position and relaxed. They lasted from fifteen to twenty minutes, irrespective of the amount of rest he had had during the night. As a rule, the patient could be aroused easily, while at other times it was difficult to awaken him. They had never occurred while he was walking or eating, but they occasionally had occurred during conversation. These periods of morbid somnolence had made it impossible for him to hold a position permanently; he had had as many as fifteen or twenty positions within the past three years, but was invariably discharged for "sleeping on the job."

The mother said that when the patient was small, the spells of "heat prostration" continued to make their appearance every summer until he was about 16 years of age, in spite of unusual care and protection. It is important to note that when the narcolepsy was well established, these so-called "heat spells" disappeared. The mother believed that the attacks occurring in childhood during the summer resembled those which he experienced following laughter. In 1918, at the age of 8 years, the patient had a severe attack of influenza and was ill for from four to six weeks. It was impossible to ascertain whether or not he had had somnolence, insomnia or diplopia at this time. There were no evident after-effects from this disease, and, according to the mother, the behavior and personality of the child were in no way affected.

The patient began school at 6 years of age and progressed normally. When he was 9, he was placed in an orphan's home for two and one-half years because of the death of his father. He later lived with an uncle and then with his mother. In August, 1927, at the age of 17, he married a girl of the same age without his mother's consent. His one child, 19 months of age, was apparently normal in every way. There had been considerable domestic difficulties and problems in his marital life. Also, recently the patient had been under a strain due to a dissension of both families on the suggestion that he be sent to an institution for epileptic patients.

The patient was 69 inches (175.3 cm.) tall and weighed 150 pounds (68 Kg.). His general appearance was normal. The skin was of normal texture. The bony framework was normal. The distribution of hair tended to resemble that of the female type. The genitalia seemed to be normally developed. The thyroid gland was palpable, but not enlarged. The pupils were about 5 mm. in diameter and responded to light and in accommodation. Other than coarse tremors of the tongue and a fine tremor of the fingers, there were no significant neurologic signs. The reflexes were not increased, but were easily obtained on both sides of the body. The test for automatic associative movements gave negative results. Although the facies was somewhat ironed out, he could draw up both corners of the mouth equally and well, without any evidence of exhaustibility or weakness of the orbicularis oris developing. There was a slight enlargement of the neck on the right side. The heart and lungs were practically normal. During the examination, the patient showed symptoms of vasomotor disturbance, such as flushing of the face and perspiration on the neck. Following the examination, the patient fell asleep. The following studies were made while the patient was under observation on the neurologic service of Dr. Winkelman at Temple University Hospital.

Laboratory studies revealed that the urine, blood count and chemical content of the blood were normal. The Wassermann and Kahn reactions of the blood were negative. Examination of the spinal fluid showed: pressure, 8 mm. of mercury; Wassermann reaction, negative; cells, 2; globulin, a faint trace, and colloidal gold curve, no change. The basal metabolic rate was minus 4 per cent.

Ophthalmologic examination showed that the media was clear, the disks were almost round, and the margin was visible, although there were remains of the nerve sheath. There was also a marked overcapillarity, as well as tortuosity of the vessels in the disk and periphery.

Vestibular tests showed a loss of function of the left vertical semicircular canal. The hearing was good in both ears. There were observations indicative of a

supratentorial lesion of the brain. A roentgenogram of the skull was negative. The sella turcica was of normal size.

During the patient's stay in the hospital, he had repeated attacks of sleep from which he could easily be aroused. He would immediately fall asleep when resting in bed. He was also observed in two cataplectic attacks, each of which followed a spasm of laughter. The muscular relaxation consisted of symptoms identical with his descriptions of this phenomenon. They lasted one minute, and the patient did not seem to suffer any after-effects. Since discharge from the hospital he had seen double on a number of occasions. The narcoleptic symptoms had decreased during that time.

In the literature it is agreed that narcolepsy and epilepsy have nothing in common. In this case, the only related symptom of a possible epileptiform nature is the history of slight injury in falling during a few of the cataplectic attacks, but there was neither loss of consciousness nor incontinence, and restrictions of fluid and the administration of phenobarbital had no affect in controlling the condition; therefore, I believe that epilepsy can be definitely ruled out.

The impulse to consider this case as a postencephalitic process in view of the history of the severe attack of influenza in 1918 is tempting; after close study this diagnosis does not seem to be improbable.

DISCUSSION

DR. MAX LEVIN: I wish to call attention to the increasing frequency with which cases of Gélineau's syndrome are being reported in the literature. Two years ago, in preparing a review of the syndrome, I found reports of 66 cases. At the present time the literature contains 120 cases. In other words, 54 cases from many different parts of the world have been recorded during the past two years.

Dr. Silverstein's case brings up a number of interesting points. The onset of the disease apparently occurred at puberty. Redlich made the statement that this condition usually makes its appearance at puberty, which was borne out by the cases that had been reported prior to Redlich's publication. The more extensive experience of recent years, however, shows that almost as many cases have begun during the third as during the second decade. While 44 cases began during the second decade, 36 cases began during the third, and 18 during the fourth.

Dr. Silverstein pointed out that at the age of 4 the patient had "heat strokes" which persisted until he was 16. During these "strokes" he apparently had some slight disturbance of consciousness. It is possible, however, that the "heat strokes" constitute an allied phenomenon.

It is of interest that Dr. Silverstein's patient occasionally harms himself during a cataplectic attack. Many authors have stated that narcolepsy and epilepsy are totally distinct from one another. Kinnier Wilson, however, has wisely warned against making too sharp a distinction until more is known about both of these conditions. In this connection it is noteworthy that Grainger Stewart recently reported the case of a child which began with typical epilepsy and later developed into the characteristic symptoms of Gélineau's syndrome. Also, B. Fisher reported the case of a patient with true Gélineau's syndrome who also had certain epileptoid phenomena — generalized convulsions sometimes developed after strong emotions (Affektepilepsie).

With regard to treatment in this interesting condition, Daniels, of the Mayo Clinic, has recently reported great success from the use of ephedrine. The early pioneers in the use of ephedrine observed that the drug not infrequently produced marked insomnia, and this prompted the investigators at the Mayo Clinic to use it in the treatment for Gélineau's syndrome. So far, they have treated five patients, and they report that within twenty-four hours after the administration of an adequate dosage, the symptoms of Gélineau's syndrome are abolished. These results are most encouraging.

DR. A. SILVERSTEIN: Heat prostration is not unusual in children, and as the patient's personality shows a marked vasomotor instability, he may have been

subject to fainting spells. I did not lay too much stress on these spells, as the mother was not certain in their description, and for that reason I did not want to label them cataplexy. Through close study of the case and the history of a severe attack of influenza in 1918, diplopia and other manifestations while the patient was under observation, I am inclined to consider this a postencephalitic condition rather than something which started early in life. Furthermore, very few cases have been reported in patients before the age of 10 years.

A Case Presenting a Unilateral Vestibular Syndrome with a Contralateral Dissociated Hemianesthesia. Dr. Joseph C. Yaskin.

While, in the main, this patient presents the essential features of occlusion of the posterior inferior cerebellar artery, yet the presence of certain fundamental signs in his condition cannot be attributed to this syndrome, and it is deemed advisable to present the case before the Society with the hope that some light may be shed on the atypical manifestations.

J. Y., a man, aged 39, a Lithuanian laborer, was admitted to the Graduate Hospital (service of Dr. T. H. Weisenburg), on Oct. 23, 1930, complaining of severe dizziness and inability to sit up. There was no history of important previous diseases or of venereal infection. He had never drunk or smoked to excess. About ten years before admission, while working in a coal mine, he was struck on the right side of the head and was unconscious for some time. He stated that there was some bleeding from the right ear, and that since that time he had heard poorly with the right ear. He made a rapid recovery, returning to work in a few days. He had since been in good health until one week prior to admission to the hospital when he had a dizzy spell, with vomiting, lasting a few minutes and necessitating his discontinuing work for the day. On October 23, while on his way to work, he suddenly became very dizzy, sat on a step of a house and called a policeman who arranged for his admission to the hospital. On admission to the hospital, he stated that he felt "sea-sick" and that he had vomited on the way to work. He also complained of inability to sit up for fear of falling and of a dull headache over the right frontoparietal region.

The patient was mentally clear and answered questions promptly and accurately. The temperature was 97 F., the pulse rate 70 and the blood pressure 120 systolic and 70 diastolic. He was well developed and well nourished. The face was rather flushed, and other cutaneous areas showed a peculiar mottling such as is often observed in subcyanosis. There was no glandular enlargement; the tonsils appeared normal; the teeth were in poor hygienic condition; there was no enlargement of the thyroid gland. Examination of the heart gave negative results; examination of the lungs showed an impairment of the percussion note in the right hilus, but no change in the breath sounds, which was considered as being due to anthracosis. The radial arteries showed evidence of fibrosis.

The patient preferred to lie on his back with his head and eyes turned sharply to the right. He could easily turn his head and eyes to the left, but this increased the dizziness to a marked degree, and he would immediately revert to the original position. There was a violent horizontal rotatory nystagmus with the fast component to the left.

The sense of smell appeared normal on both sides. He stated that his vision was blurred, objects continually turned about him and usually to the right. Examination of the fundi was unsatisfactory owing to the violent nystagmus. The right palpebral fissure was much narrower than the left, and when the patient looked upward the elevation of both upper eyelids was incomplete, more so on the left side. The right pupil was smaller than the left; both pupils were regular and responded well to light and in accommodation. Introduction of cocaine into the right conjunctival sac did not dilate the pupil. The left side of the face and neck perspired freely, while the opposite corresponding area was dry. There was no definite evidence of enophthalmos of the right side. There was a violent horizontal rotatory nystagmus, with the fast component to the left. The eyes and head were continually drawn to the right side and simulated a conjugate deviation

to the right. During these movements the right eyeball was drawn downward and to the right, while the left eyeball remained in a higher plane and somewhat outward, giving the appearance of a skew deviation. When individual extraocular muscles were tested, no weakness was detected, although the conjugate movements were much fuller in looking to the right or downward than in looking to the left or upward. There was no weakness of the masseter, temporal or pterygoid muscles. There was definite anesthesia to pain, cold and heat over the left trigeminal distribution, except for the area supplied by the ophthalmic branch. There was definite weakness on voluntary innervation of the right lower part of the face, the right nasolabial fold and angle of the mouth distinctly lagging; the upper part of the face was innervated equally well on both sides. On emotional innervation, the right side of the face contracted much better than the left. The sense of taste was unimpaired. There was considerable loss of hearing in the right ear. There was no difficulty in articulation or in swallowing both solids and liquids. The soft palate was bilaterally well innervated. There was a tendency to keep the head to the right. The tongue protruded in the midline and presented no weakness in any movement.

There was no weakness or appreciable change in muscle tonus in either arm. The biceps and triceps reflexes were bilaterally diminished. The Hoffmann sign was negative. There was total anesthesia for pain, cold and heat over the entire left upper extremity, extending to and involving the entire left side of the head. The senses of touch, movement and position, vibration and stereognosis were normal on both sides. The finger-to-nose test on the left was normal. On the right side, there was considerable zigzagging on reaching the nose, which was often missed. There was also some adiadokokinesis of the right hand, as well as past pointing.

There was no weakness or appreciable change in the muscle tonus of the lower extremities. The knee and achilles reflexes were bilaterally depressed. On one occasion, there was a doubtful Babinski sign on the right. There was complete anesthesia for pain, cold and heat over the left lower extremity. All other forms of sensibility were normal on both sides. In the knee-to-heel test there was considerable zigzagging when the right heel approached the left knee, and there was a tendency to past pointing.

There was no discernible weakness of either the muscles of the back or of the abdominal or iliopsoas muscles. The abdominal and cremasteric reflexes were normally active. On attempting to rise, however, the patient would immediately incline to the right and, despite supporting himself with his arms, would tend to fall out of bed. He had to be placed in a bed protected by side bars to avoid injury.

On October 24, laboratory investigation showed that the urine contained 0.3 per cent dextrose; it was normal in every respect on all subsequent examinations. A blood count showed: erythrocytes, 5,460,000; eosinophils, 4; basophils, 1. Chemical analysis of the blood showed: sugar, 102 mg.; urea, 9 mg.; blood plasma, carbon dioxide 62 cc. The Wassermann reaction of the blood was negative with all antigens. On October 25, the manometric pressure of the spinal fluid was 12 mm. of mercury, rising to 22 mm. on compression of the jugulars. The fluid was clear, contained 4 cells and was normal in all respects.

A roentgenogram of the skull, taken on October 24, showed that the pineal gland was normally situated. The pituitary fossa appeared normal, except for a slight roughening of the posterior clinoid processes which might be due to calcification of the ligaments.

On November 5, laryngoscopic examination by Dr. Gabriel Tucker showed: "Mirror examination shows right side of larynx to be motionless. The cord is in the midline. The appearance is that of a right posticus paralysis."

There was a definite Horner syndrome on the right side, manifested by drooping of the right upper lid, by enophthalmos and by miosis of the right pupil as compared with the left. Instillation of cocaine into the right conjunctival sac caused no dilatation. The left eye was turned up and outward, owing to amblyopia

caused by absence of the lens; the right eye was in a normal position. The condition was therefore not a skew deviation. There were no palsies of any of the extra-ocular muscles; the fundi were essentially normal. The nystagmus was pronounced when the patient looked to the left, with the quick component to the left, the slow component to the right. This was much diminished when the patient looked to the right and almost entirely absent when he looked straight ahead of him.

Bárány tests (Dr. Lewis Fisher, November 14) revealed: Hearing was good in the left ear, but impaired in the right, the deafness being of the nerve type. Spontaneous nystagmus was present when the patient looked in all directions, but especially when he looked to the right, the left and upward. The movements of the pelvic girdle were poor, especially those to the left. Nystagmus and vertigo were longer after the patient turned to the right than after he turned to the left. These observations varied from time to time. On the last examination, November 14, there was a definite disproportion in the duration of the two responses, such as, for instance, twelve seconds of nystagmus and thirty-two seconds of vertigo after turning to the left. Douching of the right ear produced prompt responses from all canals, but the nystagmus from the horizontal canal was perverted. Douching of the left ear showed that the responses were delayed, especially from the vertical semicircular canals, but were not perverted. The character of the responses definitely indicated a lesion of the brain. There was no evidence of pressure in the brain. The cerebellum appeared to be unaffected, as shown by the good vertigo responses. The lesion was apparently located in the brain stem, since the abnormal vestibular responses were largely nystagmic manifestations. A degenerative lesion of the brain stem could readily account for all of the abnormal manifestation.

The patient made a constant, gradual improvement. On October 24, the day following admission, hiccups developed which lasted almost a week and were accompanied by upper abdominal discomfort. The headache disappeared in the course of a couple of days. The nystagmus and vertigo diminished very slowly, so that on October 30, the patient was still unable to sit up in bed without falling over to the right side. On November 4, the vertigo and the nystagmus were slight, so that the patient could get out of bed and walk. He complained of weakness of the right leg when walking. On objective testing of the individual groups of muscles, there was no weakness as compared with the left side. On standing up, there was a genu-recurvatum on the right, and in walking the right heel was lifted higher than the left. Otherwise, the objective neurologic condition remained unchanged. A reexamination on November 20, showed the following: On walking about, the patient still inclined somewhat to the right, and when tired tended to fall in that direction. This was increased by walking a straight line, but was not affected by walking around a chair or closing the eyes. He swung his arms normally, and there was no disturbance in associated movements. The right knee tended to bend somewhat backward. There was still a definite Horner syndrome on the right, manifested by narrowing of the palpebral fissure, enophthalmos, miosis and dryness of the skin over the entire face and neck. There was a horizontal nystagmus on looking to the right and left, and vertical nystagmus on looking upward. On voluntary innervation, there was definite weakness of the right lower part of the face, but on emotional innervation the right side of the face was innervated much better than the left; the latter appeared to be lagging. There was diminution of hearing in the right ear. There was definite weakness of the right side of the soft palate and paralysis of the right vocal cord. There was no weakness in any of the extremities; all of the tendon reflexes were depressed, and there were no pathologic reflexes. The abdominal reflexes were absent, except that on the left lower side which was obtainable but weak. The cremasteric reflexes were not obtained. There was no appreciable disturbance in tone. The entire left side of the body, except the face, was anesthetic to pain and in appreciation of all forms of heat. All other forms of sensibility were normal throughout. The right side of the face had no form of sensory disturbance.

The cornea was sensitive to the slightest touch. The left side of the face had regained its sensitiveness to pain, heat and cold, but the appreciation was not as keen on the left as it was on the right. There was no evidence of a synergic disturbance, and the patient carried out the finger-to-nose and knee-to-heel tests perfectly.

The occurrence of a right-sided involvement of the vestibular apparatus, which by its violence strongly simulated a conjugate deviation of the head and eyes, the presence of the Horner syndrome, paralysis of the right side of the soft palate and the right vocal cord, combined with contralateral hemianesthesia and hemithermanalgesia, would locate the lesion in the dorsolateral aspect of the medulla, the area supplied by the posterior inferior cerebellar artery. However, the absence of any sensory disturbance on the right side of the face and therefore the escape of the descending root of the fifth nerve on that side is an unusual occurrence in lesions of this sort. When one bears in mind the anatomic relations of the descending root of the fifth nerve to the vestibular nuclei and the spinothalamic tracts in the upper part of the medulla, one can hardly see how it could escape. Furthermore, there remain to be explained the weakness of voluntary innervation of the right lower part of the face and the transitory presence of almost complete anesthesia of the left side of the face. The patient gave a history of an injury to the head ten years previously, with bleeding from the right ear. If the right facial nerve had been injured at that time, the entire face would have been paralyzed and the emotional innervation would not be better than the voluntary. Furthermore, on emotional innervation it was found that the left side of the face was not as well innervated as the right. In this respect, the case is reminiscent of the one reported by Dr. C. K. Mills in the *Journal of Nervous and Mental Diseases* (**39**:73 [Feb.] 1912), in which there was a hemianesthesia and hemithermanalgesia of the entire right half of the body, including the face, and weakness of the right side of the face on emotional innervation. In his case, in addition, there was evidence of dyssynergia of the left side of the body. The anatomic observations reported later by Dr. Spiller were those of an occlusion of the superior cerebellar artery with destructive lesions of the left dentate nucleus and the cerebellum above this nucleus, including the superior cerebellar peduncle. In my case, the weakness of emotional innervation of the left side of the face and the hemianesthesia and hemithermanalgesia over the entire left side of the body would simulate this case in a large measure. A case somewhat similar to that of Mills and Spiller was reported by Dr. Colin Russell at the 1930 meeting of the American Neurologic Association in Atlantic City, N. J.

From the foregoing observations, Dr. Yaskin concluded that, in the main, the lesion was one of occlusion of the right posterior inferior cerebellar artery; that there might be occlusion of the smaller blood channels higher up in the brain stem, and that the fact that the patient had had a dizzy spell a week prior to the onset of the acute syndrome favored the possibility of multiple lesions.

DISCUSSION

DR. N. W. WINKELMAN: Several years ago, in a paper on "Posterior-Inferior Cerebellar Artery Occlusion," Dr. Wilson and I reported the case of a patient who presented a picture similar to this as regards the sensory condition of the face. As far as the clinical examination was concerned, there was also complete integrity of the descending root of the fifth nerve.

In an examination of the pathologic changes in cases of this sort, one is struck by the great irregularity in the extent of the lesion. Another factor that impressed us was that in a case of this sort other vascular lesions are possible. Dr. Yaskin's patient gave a history of fracture of the base of the skull with involvement of the eighth cranial nerve. Was not the seventh nerve injured at this time?

DR. ALFRED GORDON: Several years ago, I presented to the American Neurological Association a paper calling attention to a special cerebellar sign. At that time I had about eight or ten cases, one of which was verified at operation, while the others were postmortem studies. The case that I presented showed a

special symptom; namely, whenever the patient attempted to turn his head to the side opposite the lesion, extreme headache and vertigo developed. A case of this sort, in which an operation was performed several years ago by Dr. Nassau, was due to a cyst in the cerebellopontile angle compressing the cerebellum. I wonder whether Dr. Yaskin would not entertain a diagnosis of this kind. Four or six more cases that did not come to autopsy showed this sign prominently.

DR. J. C. YASKIN: I hoped that Dr. Winkelman would answer some of my queries instead of putting more questions to me. Regarding the origin of the right facial paralysis, a fracture of the temporal bone with injury to the nerve ten years before has been considered. However, this does not look like a residual, peripheral, facial paralysis, first, because it is a rare occasion for the upper branch of the seventh nerve to be spared in injuries, and, second, because when the patient laughs the right side of the face is better innervated than the left, which is not true in peripheral paralysis. It may be that the lesion in the brain stem may have caught the central fibers of the seventh nerve prior to their reaching the nuclei of the right side of the brain stem, which would explain the existence of the central type of facial palsy. The only possible way to explain the anesthesia of the left side of the face would be by a similar involvement of the fibers over the left side of the face prior to their reaching the spinothalamic tract on the right side. That the descending root of the fifth nerve on the side of the lesion can be spared was shown by a case of W. S. Spiller (The Symptom-Complex of Occlusion of the Posterior Inferior Cerebellar Artery, *J. Nerv. & Ment. Dis.* **35**:365, 1908) and more recently in the cases of H. Merritt and M. Finland (Vascular Lesions of the Hind Brain, *Brain* **53**:290, 1930).

A CASE OF THROMBOSIS OF THE ANTERIOR SPINAL ARTERY. DR. A. M. ORNSTEEN.

This article will be published elsewhere.

NEW YORK NEUROLOGICAL SOCIETY

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LOUIS CASAMAJOR, M.D., *President, in the Chair*

THE UNEXPECTED RECOVERY OF THE FUNCTION OF THE SPINAL CORD FOLLOWING THE REMOVAL OF A TUMOR. DR. LEO M. DAVIDOFF.

An Italian, aged 52, was admitted to the Montefiore Hospital on Aug. 1, 1929, with the following history: Four and a quarter years previously he had fallen off a ladder and was unconscious for a few minutes, but was able to return to work. Three months later, he began to have numbness in the ulnar fingers of the right hand. This progressed to involve the entire right arm which simultaneously became paralyzed. The paralysis increased over a period of months to include the entire right side. But before the paralysis was complete on the right side, the left side began to be involved in a similar manner. There was considerable pain, particularly in the right arm, but also in the back and legs. Two years after the onset, he was able to walk, though with great difficulty and with very little help from the right side of his body.

One year and nine months before admission, a lumbar puncture was performed by a physician, and this procedure was immediately followed by a complete tetraplagia with absolute loss of sensation, of muscle power below the neck and of all sphincteric control. In this condition he entered the hospital.

Although the diagnosis of a high cervical tumor, probably extramedullary, was fairly obvious, the patient, basing his judgment on experience with the lumbar puncture, refused an operation or further punctures.

The symptoms remained essentially unchanged through nine months in the hospital. Finally, on May 31, 1930, that is, nearly five years after the onset of symptoms and two and one-half years after the appearance of what seemed to be an almost transverse interruption of function of the spinal cord, he submitted to an operation. A large, firm meningioma, measuring 3 by 1.5 by 1 cm., was removed from the spinal cord under the third, fourth and fifth cervical laminae. It was located more on the right side, but largely filled the canal. The cord in the bed of the tumor appeared like a piece of string. The only healthy looking tissue was on the left side, a few millimeters in diameter. The right half of the cord appeared to have undergone cystic degeneration.

The combination of the history and the conditions found at the operation made the prognosis gloomy with respect to any degree of recovery. To our astonishment, however, the patient began rapidly to regain power in the left leg and arm. Spasticity disappeared from these extremities, and the control of the bladder and later of the rectal sphincters returned, so that at the time of presentation (six months after the operation) he presented a typical Brown-Sequard syndrome with motor paresis on the right side, and a sensory loss on the left. He was able to stand, and with support was able to walk a little. The pain had largely disappeared, and improvement was still increasing.

CHRONIC RECURRENT MENINGOMYELITIS. DR. MOSES KESCHNER.

An unmarried woman, aged 32, a native of the United States, a bookkeeper prior to the illness, was presented. The medical history was unusually long, so that only essential data will be mentioned. She had measles and diphtheria at the age of 3. Menstruation began when the patient was 13 years of age; it was always irregular, but never painful. During the first nineteen months of the present illness, she did not menstruate. She was subject to colds, and got up twice during the night to urinate, which she had done ever since she could remember.

The present illness began when the patient was 16 years of age (in September, 1914), with vomiting, abdominal cramps and diarrhea, which had lasted one month before she entered the Beth Israel Hospital where an appendectomy was done without relief. Six weeks after the operation and while she was still suffering with gastro-intestinal symptoms, she began to have "sticking" pains in both lower extremities which, however, did not interfere with walking. During these six weeks she lost 30 pounds (13.6 Kg.). She was readmitted to the Beth Israel Hospital, where she was again operated on, this time for an intestinal obstruction. While convalescing from this operation she noted that, in addition to the pains in the lower limbs, she also began to experience a sensation of "stiffness" in them. Three weeks after the second operation, she was discharged from the hospital. At the end of the first week at home, she had an attack of excruciating pain over the entire back, with chills, fever and delirium; within the next few days these symptoms had abated, but she was unable to use her legs at all, and the upper extremities felt very weak. With these complaints she was admitted to the Beth Israel Hospital for the third time, five months after the onset of the original illness.

An abstract from the record at the Beth Israel Hospital shows that on this admission she presented a meningomyelitic syndrome characterized by rigidity of the neck and spine, involvement of the upper motor neurons of all four extremities, more marked in the lower limbs which were completely paralyzed, a zone of hyperalgesia at about the third thoracic segment with diminished sensation below this zone, and sphincteric paralysis. The spinal fluid was normal. The urine contained albumin, pus and epithelial cells, and some hyaline and granular casts. An examination of the blood showed 23,000 white cells, 80 per cent of which were polymorphonuclears. Roentgen examination of the spinal column gave negative results. Two weeks after admission, the meningeal signs began to disappear, and soon thereafter there was a gradual return of motor power in the upper extremities. On her discharge from the Beth Israel Hospital, seven

and a half months after this admission and one year after the onset of the illness, she had fairly good power in the upper extremities but none in the lower.

Immediately after discharge from the Beth Israel Hospital, she was admitted for the first time to Montefiore Hospital. Examination then showed: general emaciation; nystagmoid jerks on extreme lateral rotation of the eyes; lively jaw jerk; flattening of both hypothenar eminences; slight weakness of the left hand; complete paralysis of both lower extremities, with atrophy of the quadriceps and of the muscles of the legs and bilateral foot drop; pyramidal tract signs in all four limbs, with spasticity in the lower extremities and absent abdominal reflexes; positive Babinski sign and confirmatories on both sides; a zone of hyperalgesia between the third and fourth dorsal segments, below which there was hypalgesia and hypesthesia with thermal dissociation; disturbed sensibility of the joints in the left lower extremity; tenderness over the entire vertebral column; no fibrillations, vasomotor or trophic disturbances. There was also urinary incontinence. Laboratory studies gave essentially normal results.

One week after admission, typical herpes zoster developed along the cutaneous branches of the right anterior crural nerve, and there was a rise in temperature to 105 F., with an increase in the weakness of all limbs. Three months after admission, the patient showed a remarkable return of motor power in the lower limbs in spite of the persistence of the spasticity and of the wasting of muscle; the objective sensory disturbances had entirely disappeared, but there was still some vesical precipitancy. A slight action tremor was also noted occasionally in the right hand, probably due to weakness, but no ataxia.

A detailed review of the further course of the disease would be a repetition of the clinical histories of fourteen exacerbations and as many remissions. Suffice it to say that on her first admission she remained at Montefiore Hospital for twenty-two months. After discharge she remained at home for about five months, and during this period she was up and about attending to household and social duties. Then she had a relapse for which she was admitted to Montefiore Hospital for the second time, and after one year's stay in the hospital was again discharged with only slight evidences of pyramidal tract signs in the lower extremities. This time she was free from symptoms for twelve years and was able to attend to all her activities with merely some fatigue after prolonged use of the lower limbs. Following this remission the symptoms recurred in January, 1930, for which she was admitted to the Montefiore Hospital for the third time, in April. The clinical course on this admission was not different from that of the other admissions.

Summarizing, in a woman, a diffuse disease of the spinal cord developed at the age of 16, which had lasted for about sixteen years, four and one half of which had been spent in hospitals. Although a diffuse process, the brunt of the involvement seemed to be in the dorsolumbar portion of the cord. Whatever the pathologic process might have been, it had apparently affected the cord proper, its coverings, the posterior nerve roots and at least one spinal ganglion. If one considers the persistently lively jaw jerk as evidence of pontile involvement, the brain may also perhaps be regarded as participating in the pathologic process.

The course of the disease was characterized by exacerbations and remissions varying in duration and severity, the longest remission lasting twelve years. The disease was ushered in by gastro-intestinal symptoms which necessitated two abdominal operations, during convalescence from which a frank meningeal syndrome developed that was later followed by evidences of involvement of the cord. Whether these gastro-intestinal symptoms were root phenomena, or symptoms associated with the meningeal process, or the cause of the neural involvement, is difficult to say. From the subsequent course of the clinical history one may be justified in assuming that they were not the manifestations of an independent disease but bore some relationship to the neurologic condition.

A study of the progress of the disease showed, furthermore, that every exacerbation was preceded by and associated with some general symptoms, in most instances with chills, fever and gastro-intestinal disturbances. One of these exacerbations was associated with herpes zoster; two were associated with suppurative

foci, one behind the right ear and the other in the buttocks; seven exacerbations were associated with an inflammatory process in the parotid and cervical glands which never went on to suppuration; three were associated with mild infections of the upper respiratory tract, one appeared following a mild pulmonary infection, two followed lumbar puncture, and one followed the extraction of a tooth. The great susceptibility or lack of resistance of this patient to infections as well as the rapidity with which she overcame them is striking, although it is strange that after so many years she had not acquired immunity to them. The relatively prompt clearing up of the neurologic symptoms after the disappearance of the constitutional manifestations of the infections would seem to suggest some causal relationship between the two.

Unfortunately, the laboratory has never been able to supply any information as to the nature of the causative agent. The examinations of the spinal fluid and of the blood, including cultures of the blood and the spinal fluid, have given consistently negative results. There have never been any evidences, clinical or serologic, of syphilis. It would also seem that whatever the pathogenic agent may be, it is definitely not solely neurotropic; it seemed to affect mesodermal as well as ectodermal tissues.

From the clinical history and especially from the rapid, even though at times only partial, restoration of function of the involved neural structures, one may be justified in assuming that whatever the pathologic process may be, it is inflammatory and not degenerative. A study of the neural structures involved would seem to suggest that the brunt of the pathologic process is on the white substance of the cord, even though one cannot deny absolutely that perhaps there may also be some involvement of the gray matter, minimal as that may be.

In this connection Dr. Keschner referred to the group of inflammatory diseases recently described by Pette as involving predominatingly the white substance. This group is characterized clinically by an acute onset of symptoms with a marked tendency to retrogression. In a large number of cases involvement of the pyramidal tract is most prominent. Histologically, there is a loss of myelin, diffuse or focal, while the axis cylinders are generally less affected and at times entirely spared. Acuteness and intensity of the process dominate the histologic picture. In most cases there is also a mesodermal reaction indicative of an inflammatory process. The diseases belonging to this group come on acutely, at times without known cause and again after the manifestations of an acute infection (measles, varicella, vaccinia, variola, typhus, gastro-enteritis, etc.). Redlich grouped these cases under the heading of disseminated myelitis, and if there is also involvement of the brain, disseminated encephalomyelitis. He does not agree with Pette that disseminated encephalomyelitis and multiple sclerosis, especially the acute form, represent an analogous process, nor does he agree with him that disseminated encephalomyelitis can turn into multiple sclerosis. In Redlich's opinion, these two conditions represent different processes. Redlich also cited E. Mueller, who believes that the acute cases of encephalomyelitis after infections followed later by sclerotic lesions are not true multiple sclerosis but secondary sclerosis, as described by Ziegler and Schmauss. Redlich also insisted that this differentiation is at times impossible clinically. Spiller, Henneberg and others are of the same opinion, and Jakob stated that histologically the same difficulties may be encountered.

English authors limit the term encephalomyelitis disseminata to degenerative processes causing disseminated demyelinization and occurring in postvaccinal encephalomyelitis or in the exanthems.

Leyden, in 1872, and Westphal, in 1874, described patchy or disseminated myelitis in which there was involvement of the medulla and brain to a slight extent, and which Westphal called myelo-encephalitis. In some of Westphal's cases, the lesion was limited to the cord; it was a definitely transverse lesion in which, while the process was most marked at one level, it extended also in lesser intensity up and down the cord, sparing to a great extent its gray substance. A similar group of cases of disseminated myelitis was described by Henneberg, in which the clinical picture is usually that of a transverse lesion that may occasionally be

associated with amyotrophy. Clinically, it may be impossible to distinguish these cases from ordinary myelitis. According to Henneberg, this form of disseminated myelitis is characterized by the rapid disappearance of the sensory and sphincteric disturbances, the frequent onset of the disease in the form of a Brown-Sequard syndrome, the early disappearance of the tendon reflexes and the relatively common occurrence of optic neuritis.

Whereas the case presented may have some clinical and pathologic features resembling those cited thus far and those described by Hassin, Spiller and others, taken in its entirety it differs considerably from any of them; nor does it bear any resemblance to any of the cases of involvement of the spinal cord in epidemic encephalitis as described by Wimmer, Riley and others; nor does it resemble the cases of infectious radiculomyelitis described by Strauss and Rabiner.

The case presented showed a definite meningomyelitic syndrome involving practically the entire cord, which began acutely and ran a chronic course with remissions and exacerbations which invariably registered their appearance by an acute febrile disorder associated with symptoms of infection referable to other than neural components of the organism. In this sense it resembled the cases of chronic myelitis described by Gowers, according to whom the spinal cord may be the seat of a chronic inflammation which develops slowly in the course of a few or many months; the condition may also occur as a sequel to acute myelitis which instead of subsiding may persist, manifesting signs of renewed activity from time to time. It is often difficult to say whether such a condition is to be regarded as an acute myelitis that has not subsided or as a chronic inflammation beginning acutely. Such chronic myelitis may be focal, disseminated or diffuse; it may involve the whole thickness of the cord, including its coverings at a certain level (chronic transverse myelitis), or only part of it, sometimes one-half, and occasionally for a considerable extent along the cord. Arrest of the disease may occur, but complete recovery is rare.

Some observers who saw the patient presented early in the course of the disease suggested the possibility that she had a case of disseminated sclerosis. In this connection it may be emphasized that in multiple sclerosis the condition is not stationary but progressive. In Dr. Keschner's case, as far as could be determined clinically, the pathologic process in the nervous system had never affected localizations other than those involved in the first attack. With each exacerbation the symptoms and signs referable to the original localization became more acute; it was apparently a "flaring" up of an old process without involving new structures. A remission of twelve years' duration is most unusual in multiple sclerosis. Such pronounced radicular and meningeal involvement as in the patient presented is rare in multiple sclerosis, as is the appearance of so many exacerbations, each with a febrile episode. The clinical course of the case was entirely different from that of so-called acute multiple sclerosis. The determination of the possibility of the coexistence of encephalomyelitis and multiple sclerosis, as in Wohlwill's case, cannot be made without histologic examination. Finally, a case of multiple sclerosis of sixteen years' duration without involvement of the cranial nerves at any time would, as a matter of clinical experience, also be most unusual.

On clinical grounds, therefore, Dr. Keschner said that he believed he was justified in designating the case presented as one of chronic recurrent meningomyelitis, or chronic recurrent radiculomyelitis.

When examined at the meeting, the patient showed: Gait and station were possible only with assistance. The only positive objective signs were a very slight intention tremor of the right hand; bilateral pyramidal tract signs, most marked in the lower extremities, with a lively jaw jerk, hyperactive deep reflexes of the upper extremities, markedly exaggerated reflexes in the lower extremities with patellar and ankle clonus and a bilateral Babinski sign, absent abdominal reflexes, and a belt of hypalgesia between the third and seventh dorsal segments on both sides, anteriorly and posteriorly. There were no evidences of involvement of the cranial nerves. There was no temporal pallor. There were no psychic disturbances. The patient stated that she had no pains and had control of her sphincters.

DISCUSSION

DR. BERNARD SACHS: It is rather hazardous for me to attempt to interpret this case, but I may express a few thoughts that I had in regard to it. The trouble is that we are all in a state of flux regarding exactly what "disseminated sclerosis" and what "disseminated myelitis" are, and whether there is such a thing as patchy disseminated myelitis. Instead of speaking of this as a case of recurrent myelitis, so far as I can gather from the history, it is a chronic condition with a number of acute exacerbations. There are only a few diseases that can be characterized in that way: disseminated sclerosis is one; multiple cerebrospinal syphilis is another. The question really is whether one is going to call a condition of this sort disseminated sclerosis, to which I must confess there is a slight resemblance, with good reasons for adhering to that diagnosis, or whether one is going to speak of it as some form of chronic myelitis, which may be of infectious origin and is subject to recurrence. After all, in her present condition this patient has definite signs of a distinct involvement of the entire pyramidal system, so that it is largely a matter of interpretation as to whether one will adhere to the old fashioned conception of multiple sclerosis, or whether one will make this appellation cover any process that is characterized by prolonged, disseminated, patchy involvement of various parts of the central nervous system; if interpreted in that way, I think that one may speak of this case as disseminated myelitis with exacerbations and remissions. Even if there was a remission for twelve years, unless it can be positively stated that the patient did not during that period have a single symptom, not so much as an exaggerated reflex, even that long remission would not necessarily affect the diagnosis, because the one symptom that is characteristic of disseminated sclerosis is the remission with exacerbations. She has the jaw jerk, and even if some of the symptoms are absent, I think that the condition, as one sees it clinically, is characteristic of a disseminated sclerosis or a disseminated myelitis. The case is an unusual one, and I think that it is well worth presenting. I dare say that if six men discussed it, they would arrive at six different diagnoses. Is there anything characteristic about the eyegrounds?

DR. MOSES KESCHNER: They are absolutely normal.

DR. BERNARD SACHS: I know that so many conditions can be included under the diagnosis of disseminated sclerosis, but I would speak of it as that rather than as a recurring myelitis, unless you are certain that there was a definite infection preceding each attack.

DR. MOSES KESCHNER: We have seen the patient at the Montefiore Hospital several times wth fever and leukocytosis. She is just getting over the extraction of a tooth, and I dare say that in two or three weeks she will walk around the wards without symptoms.

DR. BERNARD SACHS: What is her sensory condition?

DR. MOSES KESCHNER: She has a level of hypalgesia between the third and fourth dorsal segments on both sides, anteriorly and posteriorly.

DR. BERNARD SACHS: I believe you said that in one attack she had distinct symptoms of the nerve roots.

DR. MOSES KESCHNER: Yes, with rigidity of the neck and spine. It is also worthy of note that every time she had an attack she had a leukocytosis, although we could never determine anything bacteriologically in the blood or in the spinal fluid.

DR. BERNARD SACHS: We do not know all we hope to know about the relation of infections to diseases of the central nervous system, and it would be hazardous for me to attempt to say anything more. Dr. Keschner knows more about the case than any of us do, and as time goes on he may arrive at some different conclusions.

DR. S. P. GOODHART: It is of importance to recall in this connection what pathologists have done in differentiating between the inflammatory processes within the central nervous system, that is, those involving especially and primarily meso-

dermogenic tissues, and those in which ectodermogenic or nerve tissue is the obtrusive and fundamental seat of the pathologic change. Hassin and others have firmly maintained a distinction between the more chronic process as seen in multiple sclerosis, of distinctly ectodermogenic involvement, and the myelitides with more obtrusive mesodermogenic reactions. In the interests of further researches into the two different groups with their respective pathologic distinctions, it seems to me unwise to allow an important case such as this to pass without definite differential classification. To my mind, the case presented is very different in its clinical and pathologic fundamentals from multiple sclerosis. It is far more of the nature of encephalitis or rather meningo-encephalomyelitis as one sees it complicating other acute infections such as pertussis, measles and pneumonia; one must not forget that myelitis of the nonpurulent type is a common pathologic entity, and in these cases it seems probable that a so-called toxin is the noxious agent. An important consideration is the relation between the pathologic process in the central nervous system and that within the other viscus, the parotid gland, the lungs, the intestines, etc., as the site of acute purulent or nonpurulent activity. Is the relation as to cause and effect, etiologically considered, the same as in the encephalomeningomyelitic complications of pneumonia, pertussis, measles, etc., in which the organism of the primary focus in a distant viscus is doubtless neurotropic and identical in both the initial tissue affected and in the complication within the central nervous system? Or, in cases such as that presented by Dr. Keschner, is the primary seat of the pathologic process in the central nervous system with secondary activity within tissue for which the primary organism — within nerve tissue perhaps a constant factor with periodic recurrence — has affinity? I think that the case presented is one involving primarily changes in the mesodermogenic tissue in the central nervous system, and that its pathology is distinct from that of multiple sclerosis with its dominating changes in the ectodermic tissue. I think that both as to prognosis and for the purpose of further investigation and classification, it is wise to recognize a clear distinction. Hassin, Globus and Strauss, among others, have shown that the pathology in the two classes of cases is distinct. I think that Dr. Keschner has made an important contribution to the discussion of the subject.

DR. H. A. RILEY: The same idea occurred to me as to Dr. Goodhart, and I wish to ask whether it would be possible to explain the syndrome on the basis of a susceptibility of the tissue to recurring infection elsewhere; as a reaction on the part of the central nervous system to a toxemia, rather than an inflammation in the central nervous system due to the actual localization in that system of an infectious agent.

DR. SIMON ROTHENBERG: It occurred to me that this case might be something like an epidural type of infection, rather than an intradural infection. This case indicates that one is dealing with an inflammatory process, acute at times, which later subsides and becomes recurrent again some years later. I recall having had a case of epidural infection some years ago, which I thought was going to lead to suppuration; however, it did not, but followed the course of an epidural injection for sciatica, and during that period of several months the patient had definite compression symptoms with fever, which strongly simulated this case. I wonder if one can have a chronic type of epidural infection with acute exacerbations.

DR. GEORGE H. HYSLOP: I should like to discuss further the ideas expressed by Dr. Goodhart and Dr. Riley. In this patient the rather abrupt appearance of symptoms in the central nervous system and their remarkably complete regression, in repeated episodes over a long period, suggest that there is an exudative rather than a productive inflammation in the tissues of the spinal cord. Such a tissue reaction is characteristic of allergic phenomena, and in Dr. Keschner's patient the association of each occurrence of the phenomena in the spinal cord with various infective processes elsewhere in the body leads one to suspect a susceptibility of the tissues in the central nervous system. Does this patient have either an indi-

vidual or a family stock history of allergic reactions, which would include the occurrence of migraine, hay-fever, asthma, urticaria, eczema or intolerance to food? If so, the idea of susceptibility of the tissues would have some corroboration. However, it must be kept in mind that allergic phenomena may exist in a person without the occurrence of so-called allergic phenomena in his family history.

DR. ARMANDO FERRARO: I, too, feel that Dr. Keschner's statement that his case is an inflammatory process may not be entirely correct, because, as previous speakers have mentioned, these degenerative changes of a toxic nature may be present. There has been a comparison of the type of reaction that occurs in the case presented by Dr. Keschner with other cases of encephalomyelitis occurring in measles. I think that the comparison is justified, but because of this comparison I think that the pathologic process may not be an inflammatory one. In measles, as a matter of fact, one does not see the histologic picture that one has been accustomed to call inflammation. There is a lack of infiltration with hematogenous elements, and conversely a perivascular proliferation of cells that prove with appropriate stains to be microglial elements. While the conception of inflammation stands by the old description, one cannot call this type of reaction an inflammatory one. On the other hand, there are cases of measles, like the one I had the opportunity of studying which has not yet been published, in which even the perivascular proliferation of microglia is lacking. No signs of perivascular infiltration by hematogenous cells are present, and the pathologic process is a diffuse degenerative one, involving especially the nerve cells and recalling the toxic changes that one encounters in other experimental conditions, as, for instance, in experimental lead poisoning. These facts suggest that the toxic nature of the lesion in Dr. Keschner's case is still open for discussion.

DR. LEO M. DAVIDOFF: I am glad to have heard mentioned the possibility of an allergic phenomenon in this case. Other workers have made experiments on local allergy in the eye and kidney, and I have done them in the brain. The experiment consists in the injection of a bacterial or neutral protein, as serum, into the brain, and following the sensitization in this particular area, the injection of the same protein, or if it was a mixture of protein, of one of its component parts, into the same animal intravenously at a later date. This results in a so-called inflammatory process in the originally sensitized area in the brain. If the area is extensive enough, the process is manifested clinically by convulsions in the rabbit; or if the animal is killed and sections are made, a definite change is found in the tissue of the brain that corresponds to the histologic changes seen in the skin in the phenomenon originally described by Arthus. In view of such experimental evidence, I do not see why the possibility of a local allergic phenomenon may not explain the symptoms in this case.

DR. MOSES KESCHNER: It is difficult for a clinician to be able to say definitely whether the process is inflammatory or degenerative as long as pathologists tell us that they do not know what inflammation of the nervous system is. There is apparently a constant disagreement between pathologists, and especially neuropathologists, as to what degeneration and inflammation in the nervous system really are. My belief is that this is an inflammatory process.

There is nothing in the family history and nothing in the patient herself, except the repeated attacks of suppuration and the periodic swellings of the parotids, that would suggest that there might be some allergic problem in this case.

After pathologists have settled what inflammation is and what degeneration is, this case will be found to correspond to an inflammatory type of disease. I do not believe that it is a case of multiple sclerosis, nor do I think that it fits in with any of the cases of encephalitis disseminata; there is no evidence that there is any involvement of the central nervous system above the upper part of the cervical cord, unless the exaggerated jaw jerk is interpreted as due to disease higher up. For the present, then, I would label the case, chronic recurrent meningomyelitis.

CORTICAL VISUAL AND COLOR DISSOCIATION FOLLOWING GAS (CARBON MONOXIDE) POISONING. DR. ISRAEL S. WECHSLER.

A boy, aged 12, who was overcome by gas, was unconscious for several hours, and when he regained consciousness was totally blind and unable to hear or speak. The pupils reacted normally, but he had hemorrhages in the retinas. Within a week, speech returned partly and hearing completely. During his five months' stay in the hospital he had occasional convulsive seizures with decerebrate rigidity. Since then he had remained mentally retarded and vision had returned only slightly, but he had otherwise shown gradual improvement.

On examination, the patient showed unintelligible speech, mental defect, slight signs of pallidal disease, a bilateral Babinski sign and astereognosis and loss of position and point discrimination in both hands. The pupils reacted promptly to light and on convergence; the fundi were normal; light and motion were perceived; large objects were seen with great difficulty, small ones not at all, but all colors were perceived accurately and immediately, even those of objects that were otherwise not seen.

The remarkable feature was the preservation of color vision in the presence of cortical blindness, which is the opposite of what generally occurs in all cases of loss of vision, whether central or peripheral. From the mental impairment, pyramidal tract signs, previous loss of hearing, sensory disturbances in the parietal lobe and cortical blindness, the conclusion was justified that the gray matter or surface of the brain was mainly affected, the cortex having been peeled off, as it were, by the pathologic process, sparing the white matter and particularly the basal ganglia and peripheral nerves, the very structures which are most commonly affected in carbon monoxide poisoning.

DISCUSSION

DR. SAM PARKER: Have you shown colored pictures of things or people, such as you find in children's picture books, to the patient? Since he can recognize colors so well, it would be of importance to determine whether he can differentiate colored objects well, and also whether there is agnosia or apraxia.

DR. ISRAEL S. WECHSLER: We considered that question. At one time we thought that there was some agnosia. We have concluded, however, that at present he has neither agnosia nor apraxia.

DR. S. T. ORTON: Has the patient vision enough to be a pretty good guide to his movements?

DR. ISRAEL S. WECHSLER: Partly. He will pick out some of his friends in the ward. Sometimes he will collide with things and sometimes not. Now he can find his way to the dining room. I should say that his vision has improved considerably over what it was two months ago, when he first entered the Montefiore Hospital.

DR. SYLVESTER R. LEAHY: Has he been able to do any occupational therapy?

DR. ISRAEL S. WECHSLER: No.

DR. CHARLES A. MCKENDREE: How long did the period of unconsciousness last? The statement was made that "as soon as he recovered consciousness blindness was discovered."

DR. ISRAEL S. WECHSLER: The record states that the pulmotor was used for two hours, but it is not clear how soon after that he regained consciousness.

DR. SAM PARKER: In view of the lack of records, perhaps Dr. Wechsler will permit me to say a few words about this boy. I observed him at Bellevue Hospital three or four times a week soon or immediately after he was admitted to the neurologic service there. As far as the record at that time shows, there is no definite history of any of the deceased members of the family who were in the accident, or of the boy, having been overcome with gas. When one sees the word "gas" in the title, one is inclined to think about illuminating gas. What is known is that the entire family, particularly the patient, was overcome by

smoke. This boy has been making a most remarkable recovery. It would be difficult to recognize him today unless one had seen him fairly frequently since the accident. He was in a state of extreme emaciation, desiccation and exhaustion at the time. As Dr. Wechsler correctly stated, he was in a condition comparable to decerebrate rigidity, and the progress he has been making is rather more remarkable than one is ever able to see in cases of true poisoning from illuminating gas. In Bellevue Hospital we see from three to five cases of gas poisoning every day. Some are only superficial, but frequently they are severe, and we have not seen any case in over a year and a half in which the patients have been in any condition comparable to that of this patient. On the basis of this experience I might buttress what Dr. Wechsler said regarding the visual difficulties. The usual difficulties in gas poisoning are subcortical and not cortical, and certainly not occipital. It seems to me that the clinical course, as well as the neurologic symptoms, points to a diffuse process which may be due to gas generated in the smoke rather than to illuminating gas.

DR. S. P. GOODHART: Dr. Wechsler has presented in clear demonstration a problem, and at the same time has offered what appeals as a rational explanation in what appears in the patient to be a really unique group of symptoms. In figurative expression he tells us that the patient's cerebral cortex has been "peeled off." In an analysis of the extensive intellectual obliteration of both fundamental and acquired mental growth, Dr. Wechsler's logical conception offers a far better interpretation of a possible pathologic process than any I could offer. I must take exception to his conclusion that the preservation of acute perception of color on the assumption that the cortical layers are "peeled off" substantiates his belief that color perception is contained within the cortex; one would expect the loss of this faculty. However, the color perception may lie within deeper layers of the cortex of the occipital lobe and may thus have escaped. As Dr. Wechsler says, the case offers a rich field for investigation into the question of cortical visual localization. I would emphasize another feature of this fascinating case, namely, that involving astereognosis: it presents this type of cortical agnosia for objects in most exquisite expression. Although the perception of the peripheral stimuli, touch, two point and position sense, were only slightly involved, the patient had no conception of the form, size or texture of objects placed within his grasp; the intellectual quality of stereognosis seems emphasized here. While, of course, the basal ganglia are extensively, perhaps often exclusively, involved in carbon monoxide poisoning, I was of the opinion that the cortex is not uncommonly the site of the destructive process. Perhaps Dr. Wechsler can substantiate my impression as to localization. It is a bit surprising that from the circumstances, a destructive fire, poisoning from illuminating gas, should have resulted. However, I believe that in the combustion of damp, burning wood, a noxious gas is liberated resulting in much the same form of destruction of tissue.

DR. H. A. RILEY: I have no particular discussion of the case as the situation is to me unique. I have never seen anything like it. The question that appeals to me from the clinical aspect is the localization of the function of color perception. It would seem to me, following out Dr. Wechsler's idea, that this is practically a decortication, and from the evidence presented by this patient that it might be possible to presume that there is some color perception or recognition in the more elementary structures. One knows that in the lower primates and in the carnivores, etc., the primary centers for the termination of the optic tracts are in many ways similar to the cortex. There is a definite degree of stratification, not only in the superior colliculi, but also in the lateral geniculate bodies. This has also been brought out experimentally by Brouwer's work in cutting the optic tracts and establishing lesions in the retina, as a result of which there is a definite lamellar degeneration in the lateral geniculate body. This boy would seem to me more like a thalamic animal. He is able to walk, feed himself and avoid objects, all of which are characteristic of the thalamic animal. It would seem to me that there might be some plausibility in suspecting perhaps that there may be a degree of appreciation and recognition of color in

the primary optic centers, that is, particularly in the geniculate bodies. In support of this, one might say that the thalami and the geniculates are to a certain extent protective mechanisms. They allow for the more rapid reflex reactions that take place when the pathway passes upward, into and through the cortex. Color perception is a necessary element in the protective mechanism. It is known that there is color perception in animals that have no cortex, but in which color reaction and color perception are important in the protection of life, and therefore it seemed to me that there must be a mechanism for this purpose. I think, however, that the rapidity, quickness and apparent intelligence with which the patient recognizes the various colors and shades may cast some doubt on this hypothesis. I have never had this phenomenon brought to my attention before, and consequently with patients who have had hemianopias from occipital lesions I have never thought to try to see whether they have any degree of color perception in the blind field, but I think that it would be something well worth investigating in patients with that type of pathologic process who may come under attention.

DR. RICHARD M. BRICKNER: I wish to say a word about the possibility of the occurrence, in a human being, of "decortication," such as Dr. Wechsler believes represents the lesion in the brain of this patient. A patient was brought to autopsy at the Neurological Institute last year, who had a thrombosis of both lateral sinuses. The surface of the brain was scarlet; the discoloration was most striking in the convexity, diminishing as one approached the base. As the brain was cut, it was found that this scarlet layer was no more than about one sixteenth of an inch (0.159 cm.) deep. In other words, the lateral sinuses drain only the most superficial cortical layers. If such a thrombosis were compatible with survival, and this may be the case, it would be possible to have a decortication. I wish to suggest the possibility that a lateral sinus thrombosis, instead of a selective toxemic action on the cortical cells, may underly the cortical injury in Dr. Wechsler's case.

DR. ARMANDO FERRARO: Dr. Wechsler's statement that in poisoning from illuminating gas the lesions are found mainly in the basal ganglia may apply to human pathology, but does not correspond to our observations in experimental work. At the Psychiatric Institute we have been interested in experimental poisoning with illuminating gas, and as a result of our investigations we have found that the lesions are diffuse and involve all the cortical areas from the frontal to the occipital poles. This occurrence would support Dr. Wechsler's supposition that we are dealing in his case with a functional decortication. Of the subcortical structures, the thalamus and the diencephalic centers of the vegetative nervous system seem to suffer the most. Less marked are the changes in the corpora geniculata laterales and the corpora quadrigemina, thus supporting Dr. Riley's hypothesis that there might be some color perception in the primary optic centers. The discrepancy between human and experimental pathology may reside in the fact that in our experimental work we have cut the material in serial sections and have thus been able to study the diffusion of the lesion in all portions of the central nervous system.

DR. SAMUEL T. ORTON: I am much interested in the particular type of dissociation presented in this patient because it parallels to some degree certain of the dissociations that are found in disturbances of the acquisition of language. It seems to me that there are some comparable factors in this case, but there is a complex situation here in that more than one level is involved. There is obvious evidence of difficulty in the projection tracts on the motor side, and this is equally true at the lowest level of vision. The case therefore cannot be said to be a pure visual dissociation with retention of color vision, since there is a considerable actual loss of vision as a whole, and one must make certain allowance in the interpretation for this destruction of the first level. I think it possible to account for the astereognosis and in considerable part for the lack of visual recognition of objects largely on a loss at the third level of cortical integrations, i. e., the associative level, rather than as a general diffuse cortical disease, as has been suggested. I should be interested to know if there has been any study of the auditory function

with as much detail as has been demonstrated for the visual function. Does the patient, for instance, recognize the difference between words, and is there any particular difficulty in the recognition of words beyond that which would be expected from the degree of dementia which he shows? Obviously, there has been a dementia, and clearly the general effect of this has been in the associative function which I tentatively relate to the great temporoparietal field of the brain.

One additional point that I think should be considered is that a visual loss which was chiefly macular might result in the visual agnosia that this patient shows, but without complete loss of color vision because of a lesser loss in the peripheral retina.

DR. ISRAEL WECHSLER: I purposely made the presentation brief; first, in order not to burden you, and secondly, because it will form the subject of a more extended paper.

In reply to Dr. Goodhart's criticism on the lack of logic, I think his point is well taken. If the cortex perceives colors, and if it is thrown out of function, the boy should lose color perception. The fact is that he has not done so, and the cortex certainly is affected.

The suggestion of Dr. Brickner is not a bad one. As Dr. Ferraro stated, the changes in carbon monoxide poisoning are almost universal in the brain and do not spare the meninges. They cause venous and arterial thromboses of the meninges, so that if one had a predominant lesion of that kind one might assume a secondary pathologic condition in the surface of the cortex.

The probability is that color is perceived at three levels: (1) in the retina, (2) in the primary visual centers, namely, the geniculate bodies, the colliculi and the thalamus, and (3) in the cortex. Whatever the explanation, the great importance of this case lies in the retention of color perception and the loss of vision. This contradicts all our experience, which teaches that color is lost first and vision afterward, or that color alone is lost and vision retained. I do not want to burden you with case reports, a great many of which have appeared in the literature. Experiments have been made on animals that have been kept away from colors from birth, and at necropsy after several months, sections of the cortex showed that the lower layers, especially the fifth, with its pyramidal cells, had disappeared. How much evidence that is, I do not know. The singular fact I wish to demonstrate, however, is that color perception can be preserved intact, while vision is tremendously impaired.

CHANGES IN THE SPINAL CORD IN SUBACUTE COMBINED DEGENERATION FOLLOWING LIVER THERAPY: A HISTOPATHOLOGIC STUDY. DR. CHARLES DAVISON.

Numerous reports of cases of pernicious anemia complicated by the neurologic picture of subacute combined degeneration that have improved following liver therapy are recorded in the literature. Persuaded by these reports and the personal observations of a few patients with subacute combined degeneration who benefited by liver therapy, the following histopathologic study was undertaken. The material consisted of seventeen cases of pernicious anemia with signs and symptoms of involvement of the posterior columns and the pyramidal tracts. Of these, ten patients had been under observation prior to the institution of the Minot and Murphy treatment; the remaining seven received liver and liver extract. Transverse and longitudinal sections of the spinal cord were fixed and stained for myelin sheaths, axis cylinders and glia. Only those sections were studied in which the changes were found both in the posterior columns and in the pyramidal tracts, and which presented the typical picture seen in subacute combined degeneration, viz., lueckenfeldern destruction of the myelin sheaths and the axis cylinders and poor glial response. In the sections in which the pyramidal tracts or the posterior columns alone were involved and did not present the lueckenfeldern but showed an isomorphous gliosis, the process was considered as due to a descending or ascending degeneration. The material from cases of subacute combined degeneration with no history of liver therapy was studied only for comparative purposes. Changes in the

myelin sheaths, axis cylinders and glia in these sections were compared with those from the cases that had had the benefit of liver therapy. The latter group included two cases with apparent improvement in the neurologic signs and symptoms during life. In one case, in which the patient had had a remission in the neurologic manifestations for as long as two years, transfusions of blood were also given.

The histopathologic observations were as follows: The changes in the myelin sheaths and axis cylinders in the cases of subacute combined degeneration in which the patients were treated with liver were no different from those found in the cases in which the patients were not treated. The glia, however, in the cases in which the patients were treated showed a tendency toward proliferation and condensation, and resembled in all aspects progressive glial changes, such as are seen in multiple sclerosis, tabes, etc. This process was not observed before in untreated patients with cases of subacute combined degeneration in which the glial changes are regressive.

It may be assumed that the liver therapy caused either a reduction in the hypothetic toxin or its attenuation, and therefore allowed the glia to proliferate and replace the destroyed tissue. The only effect that liver therapy may have on the myelin sheaths and axis cylinders is to cause a cessation of further destruction of these structures. In the light of present knowledge of neurohistopathology, regeneration of destroyed axis cylinders is inconceivable. This serves to explain why the changes in the myelin sheaths and axis cylinders in the seven cases in which treatment was administered were not different from those found in the cases in which treatment was not given. This observation, however, should not discourage one in the early administration of liver in cases of pernicious anemia with or without neurologic complications. By this procedure, truly enough, all one may expect is a temporary relief or a prolongation of life, which is in itself an advance on the methods employed hitherto. To succeed in delaying the further progress of destruction of the axis cylinders and to cause the formation of a glia scar in the place of "abbau" reaction is in itself an advantage.

DISCUSSION

DR. S. T. ORTON: The lack of a neuroglial response comparable to the degree of the loss of myelin in combined systemic disease is a problem that has interested me for some time, and Dr. Davison has demonstrated a definite change in this reactive factor in the course of the cases in which treatment was given. He has, however, given only one of the possible explanations for this, the disappearance of a toxin. The whole tendency toward the explanation of pernicious anemia today is that of a process of deprivation rather than an intoxication. It is now considered to be the absence of some critical food factor which gives rise to the anemia. It has been demonstrated in the past that the changes in the spinal cord of subacute combined degeneration may precede the blood picture, and it is to be assumed that the factor that gives rise to the pernicious anemia may operate primarily on the myelin sheaths. It is therefore believable that when the factor which is lacking in the diet is given late in the course of the disease it will not only correct the anemia, but also tend to check the disintegration of myelin sheaths as well, and this seems to be a possible explanation of the change in the glial reaction. If the substance necessary for the maintenance of the integrity of myelin is also necessary for glia, and if this substance is lacking to a considerable degree, one might anticipate the lack of glial response that Dr. Davidson has called a regressive change. A parallel situation is to be seen in vascular lesions of the central nervous system. When the blood supply is entirely cut off from a large area of the brain by vascular lesions of various sorts, there results a complete loss of all the tissues derived from the ectoderm, including both nerve cells with their appendages and glia cells. The tissues derived from the entoderm, however, are apparently able to maintain their integrity at a lower nutritive level than the ectodermal elements, and fibroblasts and endothelial phagocytes are to be found still living in comparatively large cysts of softening. When, however, the interference with the blood supply is of lesser degree, one finds

differential losses in the nerve tissues also. Thus, if there is a reduction in the supply of blood, but not a complete interference, the nerve cells are destroyed but the glia cells are intact, thus resulting in a typical cast of the convolution of the brain from which all essential nerve elements have disappeared and in which the glia not only have remained but also have proliferated.

A differential starvation, not of the volume of blood, but dependent on the absence of some critical food factor, might well be so severe as to prevent glial reaction during the acute phases of the disease, but under treatment might be lessened so as to permit glial scarring.

One other point that has been stressed by Dr. Davison is orderly versus disorderly gliosis. This I have been in the habit of associating with the rate of replacement. When the fibers are disappearing at a relatively slow rate, there is time for orderly replacement of the myelin sheaths by glia fibers, such as is seen in tabes. This gives rise to the characteristic "columnar gliosis." In cases in which the loss of tissue is massive, or in which the original structure was in itself of a more or less tangled nature, one finds typical disorderly glial scarring. One other possible view of the glial reaction rests on the influence of the disintegrative products of myelin on the glial response. This subject was studied in my laboratory in Iowa City some years ago, by making fractional extractions of dogs' brains and then reinjecting these fractions into the brain of another dog. It was found in such experiments that there were definite differences in the type of glial response that took place. Some types produced a tendency toward fibrous gliosis; others produced typical ameboid cells, and still a third type called out the phagocytes in considerable number. Little is known of the chemistry of the disintegration of myelin or of the products produced by such breaking down, but it is possible that such products may be produced in different quantities in different disintegrative processes, and one might therefore expect a differential glial reaction depending on the rate and character of the dissolution of myelin.

There are two points in Dr. Davison's presentation on which I should like to take issue from the standpoint of terminology. One is the use of the term "condensation of glia." As I understand it, that term applies to a shrinkage or a contraction of substances already present; and what Dr. Davison has shown is apparently not a condensation, but a new production. Moreover, he has used the term "regressive" in a sense in which I should prefer "lack of productivity." I do not think that he has entirely demonstrated that there is a regressive change in the glia, but merely that there is a lack of formation of glia cells in those areas in which he used the term "regressive." From my own cases I am inclined to believe that one does not see much loss from the normal content of the glia in typical subacute combined sclerosis, but rather an absence of the glial productivity that one would expect in the presence of so much destruction of myelin.

DR. ARMANDO FERRARO: Dr. Davison has presented facts that cannot be discussed, as they have been carefully demonstrated. The facts consist in the occurrence of progressive changes in the neuroglial elements in pernicious anemia following treatment with liver extract, as contrasting with the regressive changes of the same neuroglial elements in cases in which treatment is not given. His pictures are convincing, and the only discussion that one may be allowed to make is of the interpretation of the facts. Concerning the influence of the liver on the glial type of reaction, I should be willing to accept Dr. Davison's point of view as well as Dr. Orton's, if it were not for the fact that it seems to me that their explanation would contrast somewhat with the hypothetic influence of the liver on the glial reaction in the unripe nervous tissue. It has been proved experimentally that the function of repair in the immature nervous system is different from the function of repair that occurs in the mature nervous system. In the premature nervous system there is a lack of the progressive type of neuroglial changes. It seems as if the neuroglial elements did not have the capacity of undergoing productive changes, thus explaining the absence of any glial scar as an end-result of the function of repair. Not only the neuroglial element, but also the mesodermal tissue seems unable to perform the function that occurs in

the mature nervous system, and such an incapacity on the side of both glial tissue and mesodermal tissue to perform a normal function of repair results in the formation of cavities. Such facts have been advanced by Spatz as a possible explanation of the process of porencephaly. Now, it occurs that in the new-born infant the volume of the liver as compared with the volume of other organs is much greater than in the adult. Consistent with the larger volume there must be a more important function of this organ, and the secretion of any hypothetic hormone or nutritional substance that is found in the adult liver might be present in a larger amount in the immature person. In the presence of such a hypothetic hyperactive function of the liver in the immature person, instead of a tendency toward productive changes of neuroglia one is faced with the fact that in the immature nervous system the changes of the neuroglia occurring in the function of repair are of a regressive type. I wish to ask Dr. Davison if he has any explanation to offer for the discrepancies between his hypothesis and the facts that occur in the immature nervous system.

Another question I wish to ask is whether Dr. Davison has paid particular attention to the process of regeneration of the axis cylinders. I am interested in this question because of the statement he made that the axis cylinders do not regenerate at all. Experimental work has proved that, at least in the spinal cord, following a transverse section, there is always evidence of an attempt at regeneration of the axis cylinders. If the regeneration does not reach a practical result, it is, according to O. Rossi, because of the formaton of a connective tissue scar and a subsequent liquefaction of this scar which occurs at the site of the section. It results in the failure of the newly formed fibrils in their attempt to pass through the scar.

If Dr. Davison's hypothesis of the stimulating action of the liver on the central nervous system is correct, one might probably find pronounced action of the liver over the process of regeneration and witness more lively attempts toward the new formation of axis cylinders.

DR. CHARLES DAVISON: Dr. Orton's idea that subacute combined degeneration is a "deprivation disease" is as acceptable as the interpretation of an hypothetic toxin. I chose the latter conception simply because most students of pernicious anemia seem to agree that the agent causing the lesion of this combined systemic disease is toxic. Furthermore, the more detailed histopathologic picture closely resembles that seen in toxic myelopathy in man and in that produced experimentally. The glial changes in toxic myelopathy are identical with those observed in subacute combined degeneration (pernicious anemia). From a study of these slides, as well as from the experimental results of Lotmar, the conception of a toxic etiology appears convincing.

Dr. Orton's experimental work on the production of different types of glial response is interesting. I cannot answer with any degree of certainty what relationship exists between the type of glial reaction and the degree or rate of disintegration of the myelin.

In regard to the terminology of "condensation of glia," I gladly accept Dr. Orton's correction and shall substitute a more appropriate term. I am inclined, however, to favor the term "regressive glial changes." I should have shown a longitudinal section from a normal spinal cord stained by the Victoria blue method. The glial changes in the cases of subacute combined degeneration in which the patients were not treated with liver are much less than those observed in the normal spinal cord. For this reason this type of transformation was designated as "regressive glial changes."

Dr. Ferraro brought forth the interesting fact that in the embryo repair in the immature nervous system is different from that which occurs in the mature nervous system. In spite of the fact that in the embryo the liver is much larger and plays a greater function, in case of damage to the nervous system there is a poor glial response. This may be explained in several ways. In the first place, the observations noted in the embryo cannot always be applied to the adult. In the immature nervous system, the glia tissue is in a primitive state, and it is

possible that the influence of the function of the liver on the primitive spongioblasts may be different from that on the fully developed astrocytes, the predominating glia elements in the white matter of the adult spinal cord. Another factor that has to be considered is the functional capacity of the liver in embryonic life, when it is associated with some disorders of the nervous system. Pathologic states of the nervous system are frequently associated with diseases of the liver. Under such circumstances one may expect a poor glial response. I realize only too well that our discussion is theoretical. I have attributed to the liver the glial productivity observed in the seven cases of subacute combined degeneration, for I found it in each case, and could not find the same picture in the cases in which treatment was not administered.

Attention was paid to the process of regeneration of the axis cylinders. At first I was more interested in this phase than in the glia, for I wanted to explain the occasional favorable results reported by some investigators in the cases of subacute combined degeneration in which treatment had been given. As I have shown, the axis cylinders, as well as the myelin sheaths, were the same in the patients treated and in those not treated. There is a possibility that occasionally an axis cylinder may regenerate. This possibility, however, is remote, for the pathologic process in the combined systemic disease is not the same as in the experimentally produced transverse section of the spinal cord, where the axis cylinders are at first affected at the cut ends. Immediate approximation of such ends may lead to regeneration, but when the axis cylinder is damaged almost throughout the entire spinal cord, such a regeneration is improbable. In spite of the lack of regeneration on the part of the axis cylinders, I am in favor of the early and intensive administration of liver in cases of pernicious anemia complicated by neurologic manifestations.

THE MECHANISM OF ABNORMAL INVOLUNTARY MOVEMENTS. DR. S. C. BURCHELL.

An abnormal involuntary movement is an automatic motor act that recurs with more or less regularity as to time and as to pattern. Dr. Burchell made an attempt to explain the constant recurrence of the movement by resolving it into two components, each striving for dominance, the result being a reiterative motor act. In the group of abnormal involuntary movements are included choreoathetosis, tremor, dystonia and torticollis, to which may be added nystagmus and the convulsive state.

Nystagmus is not usually included in this group, but it is an automatic motor act that recurs with regularity as to time and pattern. In addition, infinitely more is known of its physiology than of that of the other members of this group. Vestibular nystagmus consists of a slow deviation of the eyes to the lateral position, followed by a quick return to the midline. The slow movement of the eyes to the lateral position is only part of a more general tendency of the whole organism to deviate in this direction, as shown by the falling and past pointing in the same direction. This tendency of the whole organism to deviate is a tonic postural reflex of labyrinthine origin, as shown by Magnus. The quick movement returning the eyes to the midline is part of a more general corrective tendency which prevents the body from falling; it is a phasic righting reflex. The movement in vestibular nystagmus is the resultant of a tonic postural reflex in one direction and a phasic righting reflex in the opposite. It is possible, under certain conditions, to see the tonic postural reflex uninterrupted by the righting reflex. According to Bárány, if the pathway that controls lateral gaze to, let us say, the left is destroyed and then a nystagmus is induced with its slow component to the right, the result is a tonic deviation of the eyes to the right and no interruption by a quick component, and uninterrupted posture results.

This mechanism was applied to the other members of this group. In each case there is a static and a kinetic form; that is, there are clinical forms that represent the uninterrupted posture and are static, and forms that represent the

constant interruption of the posture and are kinetic. It is frequently possible to see the conversion of the kinetic into the static form by destruction of the righting reflex.

Choreo-Athetosis.—Chorea and athetosis were considered together for obvious reasons. There is first the posture, "frozen athetosis," the "striatal foot," etc., and then the movement, which represents a constant interruption of this posture. It is well known clinically that, for the occurrence of the movement, in addition to the lesion of the basal ganglia, a functionally intact pyramidal system is necessary. In 1910, Horsley reported a crucial experiment on a patient who had athetosis of the left arm. He removed the arm center from the right motor cortex, and immediately all movement stopped. The arm, however, did not assume the hemiplegic posture, but an athetoid position. Dr. Burchell recalled the case of a woman with athetosis of the right arm who had a thrombosis of the left cerebrum so situated as to interrupt the pyramidal fibers for the arm. In her case, also, all athetoid movement stopped. To sum up, athetosis is the result of a postural reflex released by striatal destruction and its constant interruption by a phasic righting reflex of cortical origin.

Parkinsonism.—In parkinsonism there is a posture in which there is a redistribution of tonus in the direction of flexion, and a tremor that is regular as to time and pattern. Clinically, there are two types, the static and the kinetic. It is well known that a hemiplegia will abolish the tremor in parkinsonism, and the late Dr. Stephenson described such a case before this Society last year. To summarize, parkinsonism is primarily a tonic postural reflex, and the tremor results from the constant interruption of this posture by a phasic righting reflex which attempts to return the part to its normal position. This view is reminiscent of Hughlings Jackson's remark that tonus and tremor are of the same nature. Tonus is tremor run together, and tremor is tonus spread thin. According to the view set forth in this paper, tremor is interrupted posture.

Dystonia.—Dystonia is a torsion movement of a grosser type than athetosis, and involves the axial musculature, while athetosis is more marked in the appendicular structures. Little is known of the anatomic basis of this disease. Dr. Burchell limited his remarks to pointing out that again there is a static and a kinetic form of the same disorder, the myostatic and myokinetic types of Brock and Wechsler. The same formula of a postural reflex and a phasic interruption of this can be applied here.

Torticollis.—Torticollis is a dystonic movement involving the head and neck. Again there is a static and a kinetic form, the tonic and clonic forms of the systematic writers. The static form consists of a rotation of the head to one side. The kinetic form is similar to nystagmus. It consists of a slow rotation of the head to one side, followed by a quick snap back to the midline. The analogy to vestibular nystagmus seems obvious, and the formula of a tonic postural reflex in one direction followed by a phasic righting reflex in the opposite direction seems to apply nicely.

The Convulsive State.—The convulsive state may be analyzed into two components: (1) the tonic attack with generalized hypertonia, similar to decerebrate rigidity, and (2) the clonic phase, which consists of rhythmic jerks that tend to interrupt the abnormal posture and return the parts to their normal position. This continues until the normal tonic equilibrium is reestablished. Elsberg and Pike recently published a series of important experiments in which they succeeded in separating the tonic and the clonic elements. Working with convulsions produced in cats by absinth, these observers found that if they first decerebrated the animal, absinth would cause tonic fits uninterrupted by the clonic element. If they split the pyramidal decussation in animals with an otherwise intact nervous system, only tonic fits would result. If they hemisected the cord, clonic attacks would occur on the normal side, but on the operated side, only tonic fits would result. This seems to be plain evidence that if the corticospinal connection is interrupted the tonic fit proceeds uninterruptedly, and that what the cortical element of the

attack represents is a phasic righting reflex which tends to bring the part out of the abnormal posture and return it to its normal position.

To sum up the convulsive state, it is first the release of a tonic postural reflex (decerebrate rigidity) and then the interruption of this posture by recurrent phasic righting reflexes originating in the motor cortex.

DISCUSSION

DR. ISRAEL WECHSLER: I have little to add to what I consider a fine conception, one which may become fruitful, but which needs experimental work to prove it. When Dr. Brock and I discussed a similar topic with Magnus, his criticism was that the conception was probably correct, but that there is too much we do not know about righting reflexes, especially above the higher cortical centers. Dr. Burchell has advanced his speculation beyond even that we ventured. He assumes, I fear, too many things: that posture, for instance, is the result of a loss of certain elements in the basal ganglia. He makes the further assumption that posture and tonus are the same. I do not know whether I understood him correctly, but he adduced no evidence for that. The fact is that we observed changes in postures with no increase or even loss of tonus. Cases of parkinsonism have been described in which there was a hypotonia rather than a hypertonia, and yet there was the typical postural attitude. Dr. Burchell brings in tremor in association with the other ordinary abnormal involuntary movements. I think that tremor is a much lower form of movement than athetosis or chorea. The epigram he made sounds good, but I do not like epigrams in neurology as well as I do in literature. Certainly, the old epigram that tremor is tonus run thin is not true. The conception that tremor is interrupted tonus is a little more appealing, but the fact remains that there are cases of increased tremor and no tonus, others of tremor and increased tonus and still others of definite changes in posture and neither tremor nor tonus.

The matter of the cutting off of fibers of the pyramidal tract and thus destroying movement does not answer the question that Dr. Burchell postulated. All we know is that voluntary and involuntary movements are stopped by section of the upper as well as of the lower motor nervous pathways. I can follow Dr. Burchell as far as nystagmus and torticollis are concerned, and I can understand his allusion to the righting reflexes, but I think that much more work is necessary to substantiate his speculative idea, which, however, appeals to me.

DR. SAMUEL BROCK: Dr. Burchell defined an abnormal involuntary movement as an automatic act. I do not believe that involuntary movements are automatic. There is a good deal more to the reflex evocation of abnormal involuntary movements than is apparent. Certainly in the case of some dyskinesias one can modify the form of the involuntary movement by increasing the tonus of other parts. This has been described as synkinesis or "associated movement" and indicates the presence of reflex factors. Then again, torticollis brings up certain reflex possibilties that I think have not been stressed. I like Dr. Burchell's inclusion of torticollis in his discussion. At a subsequent meeting I hope to analyze some of the reflex characteristics of torticollis.

At present I have a patient under observation who has had torticollis for twelve years. He was carefully studied by a psychiatrist and was successfully hypnotized a number of times. No neurotic background could be established, and his case was correctly regarded as an instance of organic disease. The movement is stopped by the application of gentle pressure on the back of his head, whether by his hand or by any other object. This seems to me to be related to the righting stimuli described by Magnus, of the type designated as "body surface acting on the head." Moreover, in the same patient the clonic and tonic elements of the torticollis become much more marked when he flexes his head far forward, a fact that leads me to believe that the tonic stimuli to the neck in the Magnus sense reflexly affect the torticollis. Foerster's operative results in a number of cases lend weight to this idea. He has described the benefit following transection of the upper four cervical posterior roots on the side opposite the active sternocleidomastoid muscle, together

with the latter's spinal accessory nerve. These are the very roots that carry the tonic neck impulses underlying Magnus' tonic neck reflexes. All of these facts relate torticollis to a tonic neck and "righting" reflex activity. As far as nystagmus and torticollis are concerned, I am in close accord with Dr. Burchell's point of view. But when he extends the use of the term "righting reflex" (first introduced by Magnus) over so wide a field, I wish to register certain objections. Magnus limited the righting reflex to a mechanism by which an animal was able to resume its optimal posture when there was a departure from it. He carefully described the stimuli underlying this righting mechanism. They came from: (1) the labyrinths, (2) the body surface acting on the head, (3) the body surface acting on the body, (4) the neck-axial muscles and (5) the eyes. I am unable to subscribe to the broadening concept of the righting reflex so as to include the phasic movements discussed by Dr. Burchell. He would have us believe that the kinetic squirming of athetosis is an attempt to "right" the athetotic posture. I cannot view the matter in this light.

When it comes to the parkinsonian tremor, I think that Dr. Burchell and I have very different ideas. I do not see how the tremor of paralysis agitans can "right" the postural disturbance. In the first place, one knows of certain cases of parkinsonism, especially the unilateral variety, in which no postural abnormality is noted, yet there may be a marked tremor. What then, is the tremor attempting to "right"? If there is no dissolution of erectness (Kraus) the tremor can hardly be regarded as a "phasic righting reflex." Moreover, I find that Dr. Burchell is perpetuating one of the few errors made by the great master, Hughlings Jackson. Tremor and hypertonus are independent phenomena. This was proved by Walshe (The Muscular Rigidity of Paralysis Agitans, *Brain* **47**:159, 1924). He abolished parkinsonian rigidity in various parts by intramuscular injections of a 1 per cent solution of procaine hydrochloride. The limbs became flaccid; the tremor was unaffected. He stated that "tremor is a phenomenon essentially different in its origin and nature from rigidity, and the widely held view that 'tremor is rigidity spread out thin' must be regarded as wholly untenable."

Following S. A. K. Wilson, I am forced to believe that tremor is a low form of abnormal involuntary movement, mediated by the anterior horn cells under the influence of a peculiar release or redistribution of nerve energy; I so stated on a former occasion (ARCH. NEUROL. & PSYCHIAT. **23**:185 and 200 [Jan.] 1930).

As to the convulsive state, I do not know how one can say that the clonic movements represent an attempt to return the part to a normal posture.

To apply Dr. Burchell's simple formula to so diverse a group of clinical pictures seems unwarranted by the facts. I think that as far as nystagmus and torticollis are concerned, Dr. Burchell has made a step forward.

I was hoping that he would accomplish a difficult feat, i. e., tell us where abnormal involuntary movements originate. I fear that the concept of "inhibition and release" has been much overworked. Might it not be a matter of the abnormal redistribution of neural energy from a diseased defunct unit to another functionally related, but normally active one? A stream of unphysiologic riotous impulses now passes through and produces the abnormal involuntary movement. This old idea of Hughlings Jackson has recently been revived by Pike and his co-workers.

Nevertheless, I want to remark on Dr. Burchell's courage in attempting to storm one of the impregnable citadels of neurology. If he has succeeded in part, he is to be praised; if he has failed in part, then he has succumbed as have many of his predecessors.

DR. J. NOTKIN: I wish to draw Dr. Burchell's attention to the fact that the clonic phase is not present in all instances of convulsive states. In many cases the clonic movements are entirely absent.

DR. S. C. BURCHELL: Dr. Wechsler's objection is well taken and is logical. When he says that the fact that none of these movements occurs when the pyramidal system is interrupted because no movement is possible without the

pyramidal system, he means, of course, that the corticospinal tract is the final common pathway for all movement. But this does not seem likely for many reasons. Thalamic preparations in lower animals are capable of extremely complicated movements. Anatomically, it is difficult to understand how a movement admittedly originating in the basal ganglia, as athetosis, could be projected on the cortex for its final common pathway, when there are no striocortical fiber connections. When Dr. Brock says that he thinks that abnormal involuntary movements are not automatic but reflex, he has undoubtedly confused the terms automatic and spontaneous, as one of the main objects of this paper was to demonstrate that they were of reflex origin, and that is, of course, what automatic means, as the automatic bladder or spinal automatism. In citing Walshe's experiment, which was an attempt to deafferent an arm, Dr. Brock is confusing tonus and hypertonus. He is also guilty of the same error in citing the instance of hypotonic parkinsonism. What he loses sight of is the fact that abnormal posture can result from hypotonus as well as from hypertonus. And though Walshe did reduce the amount of tonus in the arm by partly deafferenting it, he did not change the tendency to abnormal posture which was determined by a central mechanism. Tonus is the raw material with which posture is molded, and the posture results from the relative distribution of this tonus in the agonists and antagonists about the joints of the extremities. In this paper I merely wished to call attention to a simple mechanism that seems applicable to a large series of neurologic phenomena.

Book Reviews

DIE ORGANISCHEN EINSCHLIESSLICH DER EXOGENEN REAKTIONSTYPEN. (ENTWURF EINER PSYCHIATRISCHEN SYNDROMENLEHRE AUF KLINISCH-BIOLOGISCHER GRUNDLAGE.) By PROF. DR. H. KRISCH. Price, 13.20 marks. Pp. 146. Berlin: S. Karger, 1930.

On the grounds of an "empiric dualism," the author presents a second edition and further development of "The Symptomatic Psychoses and Their Differential Diagnosis" (S. Karger, 1919). It is an expansion of Bonhoeffer's conception, doing better justice to the more subacute and chronic disorders, and being devoted to a generic description with subordination of the etiologic differentiations. After a historical and critical introduction, he takes up the general concepts: causes and their quantity and quality; symptoms, syndrome and disease entity; the constitutional disposition; localization; "endogenous" and "exogenous"; the rôle of the premorbid personality, and the influence of age and sex. The chapter on the organic and exogenic reaction types considers the encephalasthenic (neurasthenic) syndrome, the organic alteration of consciousness, the delirious syndrome, the psychomotor symptoms, the hallucinatory syndrome; moreover, the affective and the paranoid reactions, the organic alterations of the personality, the dementias and early acquired defects. He gives a brief special discussion of perplexity, flight and confusion, lack of initiative and the amnestic Korsakoff syndrome. He recognizes a great diversity of mixtures of various elementary symptoms, changes not only of intensity but of different sets of combinations; a division into primary symptoms (dementia, disorders of consciousness, Korsakoff) and secondary (variable, psychomotor, psychosensory) and tertiary (intrapsychic) ones; he uses the fiction of disease units largely in order to indicate the etiology. Bonhoeffer's exogenic reaction types do justice only to the more acute and coarse types of damage, while Krisch also includes epileptic, manic-depressive and schizophrenic components. He combines to some extent principles of localization and intensity, in harmony with Spielmeyer's vasomotor theory and Vogt's pathoclisis.

Krische reviews Zador's experiments with mescaline, etc. He gives case records of hyperkinetic motility psychosis in tumor of the brain, two psychoses in chorea, a recurrent symptomatic amentia; psychomotor excitement with cardiac decompensation; akinesis after cranial injury, and with myxedema; further, under the heading of hallucinatory syndromes, an hallucinosis following operation on the gallbladder and one after typhoid. Of affective syndromes, he gives a depression following influenza; an anxiety-state with delusions of reference accompanying chronic nephritis; a stupor in a puerperal state with mastitis; a mania-like exogenic psychosis with an abortion and infection; a depression complicated by a migrainous state; a manic-hyperkinetic state with a convulsion, and another with chorea; then the paranoid reactions, and finally epilepsy and cases of dementia paralytica with manic and schizophrenic pictures. A bibliography covers the more recent literature.

INNERE SEKRETION UND PSYCHISCHE PROZESSE. By DR. W. N. SPERANSKI. Price, 12 marks. Pp. 150. Berlin: S. Karger, 1929.

Speranski's monograph is an extraordinary formulation of what can be called only ideology of the Russian school of reflexology. It is remarkably devoid of contact with the world of psychiatry as seen and worked with in America. It is a world, one might say, of paralogical preoccupations. It aims to cover so many items that it is certainly worthy of attention as a nationalistic development. Whether it is scientifically distinctive is another question. The monograph is

translated from various publications in Russian appearing from 1923 to 1926. Speranski gives the following summary:

The first part of the book is devoted largely to the question of the development and structure of the "reflectory ascending and rebound waves," and "the reflectory-hormonal waves," the interchange of which constitutes the life activity of man, and moreover to the question of the "neurogenic-hematogenic correction," i. e., the question of the control of feeling over thought and of thought over feeling.

The second part considers two broad nosological groups, the hysteric and the catatonic, which are presented as reciprocal antipodes, and it makes plain the significance of coordination complexes which are conditioned by the "self-inhibition of the impulse" in the arousal of various reactions (impulsive, normal and negativistic) to external stimuli, as in the development of the two fundamental types of decoordination in the emotiogenous systems: the hysterical and the catatonic. The chapter on "emotional ataxias" deals with the schizophrenic disorders as the third type of disorders of coordination in the emotiogenous systems (a combination of the hysterical and the catatonic decoordination).

Finally, there is considered the question of neurasthenia (impulsivity and general tonus) and the formation of the character in the process of the social revolution.

Unfortunately, the full text is not much closer to the facts one is familiar with, hence the reviewer's characterization of the volume as a source-book of ideology.

HANDBUCH DER GEISTESKRANKHEITEN. Volume 11. Die Anatomie der Psychosen. Edited by W. SPIELMEYER. Price, 184 marks. Pp. 1136. Berlin: Julius Springer, 1930.

This book is part of Bumke's "System of Mental Diseases." It is edited by Spielmeyer and includes contributions by Spielmeyer, Weimann, Spatz, Steiner, von Braunmühl, Jakob, Jahnel, Neubürger, Grünthal, Scholz, Josephy, Schob and Hallervorden. Spielmeyer has contributed a remarkably clear and concise introduction on the anatomic investigation of mental diseases, and in his usual scientific manner analyzes clearly the advances and shortcomings of our knowledge. Spatz contributes an excellent chapter on encephalitis. He defines clearly the term encephalitis, discards from the group many pseudo-encephalitides, and presents a clear study of the entire encephalitic group. Spatz has made a distinct contribution by his recent studies of the distribution of the lesions in the encephalitides, viz.: epidemic encephalitis, rabies, poliomyelitis and Borna's disease. In this monograph he elaborates on these studies. His contribution cannot be reviewed at length here, but it is a careful study and analysis, and a fine review of the entire subject of encephalitis. Jakob's chapter on "Syphilis of the Brain and Its Membranes" is a clear exposition, and his classification of vascular syphilis a good one. Much of his chapter is given over to the gummatous formations in the meninges and brain. Jahnel has written a clear, orderly and exhaustive review of dementia paralytica. His discussion of the spirochete in relation to dementia paralytica is particularly valuable, though the entire chapter is good. Neubürger's chapter on arteriosclerosis, Grünthal's on senile dementia and von Braunmühl's on Pick's disease are good studies. Schob has written a good monograph on idiocy, and Hallervorden's contribution on diseases of the basal ganglia is clear.

On the whole, the volume is an excellent contribution. The contributors have been well selected, and the subject matter is covered thoroughly and critically. It can be recommended highly, and should be in the hands of both neurologists and psychiatrists. The book fills a definite gap in our knowledge in a manner that should please even the most critical.

NOUVEAU TRAITÉ DE PSYCHOLOGIE. By GEORGES DUMAS. Volume I. Price, 75 francs. Pp. 425. Paris: Félix Alcan, 1930.

The first volume of a new nine volume treatise, taking the place of the two large volumes of 1923, promises a most interesting presentation of French psychol-

ogy by forty-four writers, in seven volumes for normal and two volumes for abnormal psychology.

Perrier opens the discussion of the "preliminary concepts" with a new chapter of 50 pages on the structural evolution and phylogeny, and P. Rivet with one on the data of anthropology and ethnology, and Champy contributes one on the problems of growth and the physiology of the ages and sexes. Replacing the more morphologic chapter of Langlois, L. Lapicque now offers the general physiology of the nervous system and the revised and extended discussion of the weight of the brain and intelligence; A. Tournay expands his special physiology of the nervous system, and Henri Wallon deals with the biologic problem of consciousness, with considerable attention to the new data. With this background of 330 pages, G. Dumas opens the "Introduction to Psychology," and André Lelande reviews the various objects and methods of psychology, with a new section on sensations and "formes," and one on behaviorism and concrete psychology.

Even if the work promises to be rather kaleidoscopic, each article, of approximately fifty pages, permits reasonable freedom to each author to give a well rounded conception of the personal point of view and of the specific topic. It is to be hoped that the collection will come to fairly early completion.

PSYCHIATRIE. By ANDRÉ BARBÉ. Price, 16 francs. Pp. 195. Paris: Masson & Cie, 1930.

This clearly written introduction to psychiatry aims to give in 195 pages what a clinical examination of the mental condition has to add to the resources of general medical examination. Barbé begins with the reasons for which a patient or his friends come to consult a physician, the approach and a fairly detailed outline of examination of the specific mental, physical and biologic topics (100 pages). In the remaining 60 pages he recommends a "classification d'attente" and not a systematic set classification, but really uses an etiologic grouping, with a very summary statement of each disorder: (*a*) disorders related to an arrest of congenital or early development (idiocy, imbecility, debility); (*b*) disorders due to an intoxication (alcohol, morphine, cocaine, lead, etc.); (*c*) disorders due to an infection (syphilis, dementia paralytica, mental confusion); (*d*) disorders due to an organic lesion (epilepsy, cerebral tumors, hebrephrenic, catatonic and senile dementia); (*e*) constitutional disorders, so called, and those of unknown nature (mania, melancholia, periodic psychosis, chronic hallucinatory psychosis, delusions of persecution by interpretation).

This approach may have its practical justification, but it does not lead the student to a truly plastic and constructive psychopathology. As a matter of fact, it tends to foster a rather formal diagnostic interest with little outlook toward the problems and opportunities for readjustments.

PSYCHOTHERAPIE BEI ORGANISCHEN ERKRANKUNGEN. By DR. MED. FRITZ MOHR. Price, 4.80 marks. Pp. 103. Leipzig: Georg Thieme, 1930.

The author of one of the most satisfactory presentations of "psychophysical treatment methods" (Leipzig, S. Hirzel, 1925) gives in this concise and attractive booklet a clear and useful outline of what is worth while. After a survey of the influence of the physical systems on the mental processes and vice versa and the fundamentals of the psychophysical reciprocity, he discusses the methods starting from the physical side (medicaments and physical stimuli) and those starting from the mental side (hypnosis, psychoanalysis, waking suggestions, explanation and volitional treatment). He discusses the problems and opportunities presenting themselves in the management of the patient's attitude and personality in the infectious diseases (pneumonia, pulmonary tuberculosis, typhoid), in cholecystitis, bronchial asthma, organic heart disease, angina, essential hypertonia, arteriosclerosis, and the organic nervous diseases, the gastro-intestinal disorders, kidneys, arthritis and the endocrines, pains, etc. In a field in which individualization and

individual ingenuity are so important, brevity of presentation has a real merit. The clearing up of misunderstandings and fears, and the tendency to hypochondriacal utilization of the complaints and the evaluation of treatments of largely suggestive value as well discussed, and especially, also, the precaution against habit formations of various treatments and medications.

DIAGNOSTIC ET THÉRAPEUTIQUE ELECTRO-RADIOLOGIQUES DES MALADIES DU SYSTÈME NERVEUX. By A. ZIMMERN and J.-A. CHAVANY. Price, 14 francs. Pp. 639. Paris: Masson & Cie, 1930.

This book of more than 600 pages gives an excellent up-to-date point of view of the present diagnostic and therapeutic treatment for neuropsychiatric conditions. It is divided into four parts. The first part deals with electrodiagnosis, and includes such unusual subjects as chronaxia, vertigo and electromyography, discussions of which are usually not found in books of this sort. The second part is concerned with radiodiagnosis. This is beautifully illustrated and deals with the usual methods of diagnosis of lesions of the brain and cord, including the results of the injection of air, iodized oil, etc. The third part deals with methods of treatment, including the use of the x-rays, radium, etc. It is interesting that the chapter dealing with radiotherapy is headed "curietherapy." This would be expected in a French book and is eminently fitting. The fourth part has to do with diseases of the nervous system. It is divided into five parts: (1) diseases of the brain, (2) diseases of the spinal cord, (3) the peripheral nerves, (4) diseases of the muscles and (5) paraneurologic syndromes, such as goiter, tetany, hysteria, writers' cramp and similar conditions, neurasthenia and asthenic conditions. The book is well illustrated and is an interesting exposition of the modern French point of view.

SELECTED READINGS IN THE HISTORY OF PHYSIOLOGY. Edited by JOHN F. FULTON, M.D. Price, $5. Pp. 317. Springfield, Ill.: Charles C. Thomas, 1930.

It was a delightful thought that impelled the editor to publish this readable volume. As stated in the preface, it was Long's attractive "Readings in Pathology" that suggested to Fulton the preparation of a similar volume on physiologic subjects. The chapters on the muscles, peripheral nerves and the central nervous system will be of particular interest to neuropsychiatrists. However, the other chapters are of equal importance and interest; for example, Pavlov's "Work of the Digestive Glands" and his subsequent work on the nervous system. The editor has made excellent selections, and his biography of the authors is delightfully presented. It is hoped that some enterprising neuropsychiatrist will publish similar selected readings in the history of psychiatry and neurology.

ÉTUDES NEUROLOGIQUES. FOURTH SERIES. By GEORGES GUILLAIN and T. ALAJOUANINE. Price, 65 francs. Pp. 358. Paris: Masson & Cie, 1930.

This is the fourth volume of reprints of work emanating from the Neurological Clinic of the Salpêtrière in Paris. The three previous volumes, which appeared in 1922, 1925 and 1929, were also reviewed in the ARCHIVES. The present volume comprises a number of articles under the following headings: (1) Nervous Semeiology; (2) Pathology of the Brain; (3) Pathology of the Cerebellum, Cerebral Peduncles, Protuberance and Bulb; (4) Pathology of the Spinal Cord; (5) Pathology of the Cranial and Spinal Nerves; (6) Epidemic Encephalitis, Postencephalitic Parkinsonian Syndromes; (7) Miscellaneous.

There are thirty-two articles, many of which have been abstracted in the ARCHIVES as they originally appeared in the current French literature.

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